# Building Carbohydrates on Dioxanone Scaffold

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By

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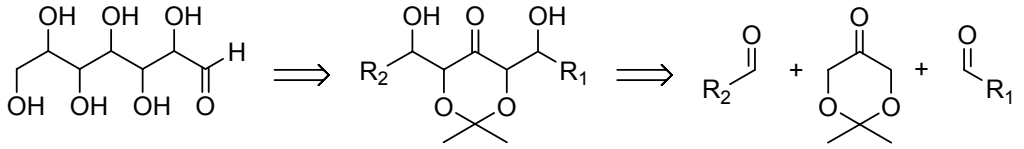
# ABSTRACT

Protected DHA units, known as dioxanones, are interesting compound which can be used as the building blocks for synthesis of polyoxygenated natural products. The direct aldol reaction is employed for converting of those inexpensive starting materials into enantioenriched products of complexed structures. The double aldol strategy is used as a method to obtain higher sugars according to the scheme shown below:




The stereocontrol in the first aldol reaction is achieved by using organocatalysis. Second aldol reaction is conducted by lithium enolate chemistry leading to *anti–cis–anti* aldols as a major isomer. On the other hand boron chemistry provides *anti–trans–anti* products. This strategy is used for synthesis of higher sugars.

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I would like to take this opportunity to express my gratitude to those people who have made my stay in Saskatoon enjoyable and unforgettable.

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# DEDICATION

*I would like to dedicate my thesis to the most important person in my life:*

*my beloved husband and best friend ever*

***Grzegorz***

*for his ongoing support, love and absolutely everything*

*that I could experience with him in my life*

# TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF SCHEMES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| α | observed optical rotation in degrees |
| [α] | specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are understood) |
| Ac | acetyl (ethanoyl) |
| $Ac_2O$ | acetic anhydride |
| AcOH | acetic acid |
| aq | aqueous |
| AIBN | 2,2′-azobisisobutyronitrile |
| Ar | aryl |
| 9-BBNOTf | 9-Borabicyclo[3,3,1]nonane |
| Bn | benzyl |
| BORSM | based on recovered starting material (referred to isolated yield) |
| bp | boiling point |
| br | broad (spectral) |
| Bu | butyl |
| $Bu_2BOTf$ | dibutylboryl triflate |
| Bz | benzoyl |
| Chx | cyclohexyl |
| $Chx_2BCl$ | dicyclohexylboron chloride |
| CI | chemical ionization |
| $Cp_2BOTf$ | dicyclopentylboryl triflate |
| $^{13}C$ NMR | carbon - 13 nuclear magnetic resonance |
| COSY | correlation spectroscopy |
| CSA | camphorsulfonic acid |
| Cy | cyclohexyl |
| δ | chemical shift in parts per million |
| dba | dibenzylideneacetone |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DCM | dichloromethane |

| | |
|---|---|
| DDO | dimethyldioxirane |
| de | diastereomeric excess |
| DEAD | diethyl azodicarboxylate |
| DFC | dry flash column chromatography |
| DHA | 1,3-dihydroxyacetone |
| DHAP | 1,3-dihydroxyacetone phosphate |
| DIBAL-H | diisobutylaluminum hydride |
| DIPEA or DIEA | *N,N,*-diisopropylethylamine |
| DMAP | 4-(*N*,*N*-dimethylamino)pyridine |
| DME | 1,2-dimethoxyethane (glyme) |
| DMF | dimethylformamide |
| 2,2-DMP | 2,2-dimethoxypropane |
| DMP | Dess - Martin periodinane |
| DMSO | dimethyl sulphoxide |
| dppe | 1,2-Bis(diphenylphosphino)ethane |
| dr | diastereomers ratio |
| DRIFT | diffuse reflectance Fourier transform infrared |
| ee | enantiomeric excess, for a mixture of two enantiomers *R* and *S*, ee is calculated from equation : ee=([*R*]-[*S*])\|/([*R*]+[*S*]) x 100% |
| EI | electron impact ionization |
| er | enantiomeric ratio |
| eq | equivalent(s) |
| Et | ethyl |
| $Et_3N$ | triethylamine |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| FCC | flash column chromatography |
| FT | Fourier transform |
| H-bonding | hydrogen bonding |
| $Eu(tfc)_3$ | shift reagent, Europium tris[3-(trifluoromethylhydroxy-methylene)-(-)-camphorate |

| | |
|---|---|
| HMBC | heteronuclear multiple bond correlation (2 and 3 bond *J*CH correlation with inverse detection) |
| HMQC | heteronuclear multiple quantum coherence (1 bond *J*CH correlation with inverse detection) |
| $^1$H NMR | proton nuclear magnetic resonance |
| HPLC | high - performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum correlation |
| *i*-Bu | isobutyl (2-methylpropyl) |
| *i*-Pr | isopropyl |
| IR | infrared |
| *J* | coupling constant (in NMR spectrometry) |
| KDN | 2-keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid |
| KDO | 3-deoxy-D-manno-oct-2-ulosonic acid |
| LA | Lewis acid |
| LAH | lithium aluminum hydride |
| LB | Lewis base |
| LDA | lithium diisopropylamide |
| LHMDS (LiHMDS ) | lithium hexamethyldisilazane, lithium bis(trimethylsilyl)amide |
| LiCl | lithium chloride |
| Lindlar catalyst | palladium catalyst ($Pd/CaCO_3$) deliberately poisoned with lead |
| LRMS | low resolution mass spectroscopy |
| *m*-CPBA | 3-chloroperoxybenzoic acid |
| m | multiplet (spectral); meter(s); milli |
| $M^+$ | parent molecular ion |
| max | maximum |
| Me | methyl |
| MeCN | acetonitrile |
| MeLi | methyllithium |
| MeOH | methanol |
| MOM | methoxymethyl |

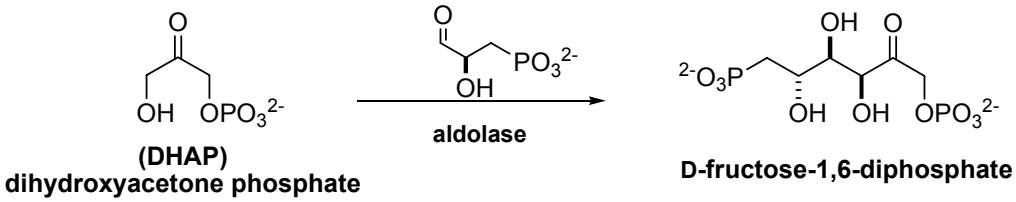
| | |
|---|---|
| mp | melting point |
| MS | mass spectrometry |
| *m*/*z* | mass-to-charge ratio |
| MS 4A | molecular sieves 4Å |
| MsCl | methanesulphonyl chloride |
| MTPA | 2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid |
| MTPACl | 2-methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride |
| NaOAc | sodium acetate |
| NBS | N-bromosuccinimide |
| *n*-BuLi | *n*-butyllithium |
| *n*-BuMgCl | *n*-butyl magnesium chloride |
| NMM | N-methylmorpholine |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser enhancement |
| OAc | acetate |
| OTf | trifluoromethanesulfonyloxy ($CF_3SO_2O$) |
| PCC | pyridinium chlorochromate |
| Pd (C) or Pd/C | palladium metal dispersed on a charcoal support |
| PDC | pyridinium dichromate |
| Ph | phenyl |
| Phtf | phtalimide |
| PMP | *para*-metoxyphenyl |
| ppm | part(s) per million |
| PPTS | pyridinium *para*-toluenesulfonate |
| Pr | propyl |
| PTLC | preparative thin layer chromatography |
| *p*-TsOH | *p*-toluenesulfonic acid (4-methylbenzenesulfonic acid) |
| Py | pyridine |
| RAMP | (+)-(*R*)-1-Amino-2-(metoxymethyl)pyrrolidine |
| Ra/Ni | Raney-nickel |
| Rf | retention factor (in chromatography) |

| | |
|---|---|
| rt | room temperature, usually 20-22 °C |
| s | singlet (spectral) |
| SAMP | (+)-(*S*)-1-Amino-2-(metoxymethyl)pyrrolidine |
| SCC | short column chromatography |
| sat. | saturated; as in a saturated aqueous solution |
| t | triplet (spectral) |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS or TBS | *tert*-butyldimethylsilyl |
| TBDMSCl or TBSCl | *tert*-butyldimethylsilyl chloride |
| *t*-Bu | *tert*-butyl |
| *t*-Boc | *tert*-butoxycarbonyl |
| TEMPO | 2,2,6,6-tetramethylpiperidinooxy, free radical |
| temp | temperature |
| TFA | trifluoroacetic acid |
| TFAE | 2,2,2-trifluoro-1-(9-anthryl)ethanol |
| *t*-Bu or *tert*-Bu | *tert*-butyl (1,1-dimethylethyl) |
| *t*-BuLi | *tert*-butyllithium |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TIPSOTf | triisopropylsilyl trifluoromethanesulfonate |
| TLC | thin-layer chromatography |
| TMS | trimethylsilyl; tetramethylsilane |
| TMSCl | trimethylsilyl chloride(chlorotrimethylsilane) |
| TMSOTf | trimethylsilyl trifluoromethanesulfonate |
| $Tf_2O$ | trifluoromethanesulfonic anhydride, triflate anhydride |
| Ts | *para*-toluenesulfonyl (tosyl) |
| TS | transition state |
| v/v | volume per unit volume (volume-to-volume ratio) |

# CHAPTER 1

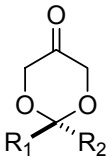
## 1. Introduction: Chemistry of dioxanones – a literature review

1,3-Dihydroxyacetone phosphate, known as DHAP, is used in Nature as the nucleophile in various aldol reactions catalyzed by enzymes. One of the most significant examples of such a reaction is photosynthesis. In this process D-fructose, a simple natural product, is formed in just a few steps from DHAP (Scheme 1.1).[1]




**Scheme 1.1**

For years researchers have been trying to find synthetic equivalents of DHAP with the aim of employing them practically, as their applicability in organic synthesis does not have to be limited just to aldol reactions. Dioxanones, the simplest ketose derivatives, can be envisaged as ketal protected dihydroxyacetone units (Figure 1.1).




**1a**: $R_1=R_2=Me$
2,2-dimethyl-1,3-dioxan-5-one

**Figure 1.1** Structure of 2,2-dimethyl-1,3-dioxan-5-one

Our group was one of the first that popularized dioxanones in synthesis and was successful in synthesis of frontalin[2] and of the protected form of carbohydrates e.g. D-

glycero-D-manno-2-octulose.[3] The power of these building blocks has also been demonstrated in several other target-oriented syntheses accomplished by Funk[4, 5] Enders,[6] Alonso,[7] and others. Some of the examples are outlined in Figure 1.2.

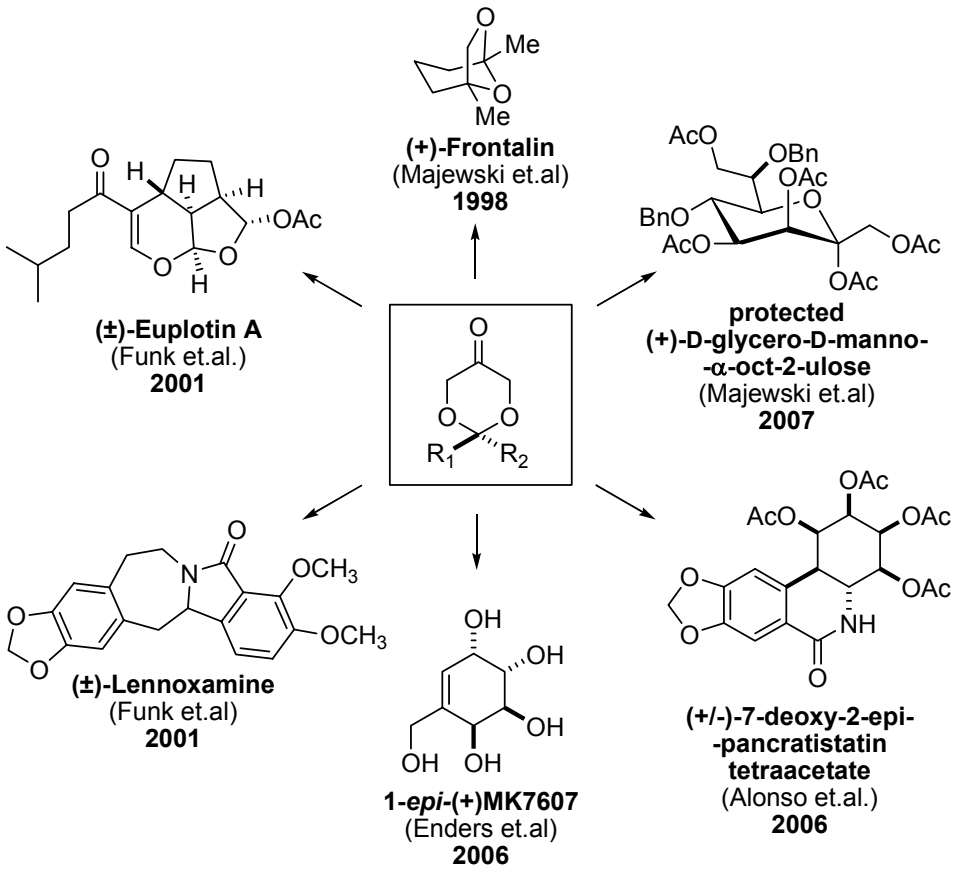



**Figure 1.2** Dioxanones in synthesis of natural products: selected examples

This introduction will focus on the use of 2,2-disubstituted-1,3-dioxanones as synthetic building blocks, with emphasis on their reactivity as nucleophiles (d-2 reagents)[8] but it should be noted that some dioxanone derivatives, most notably the chiral hydrazones are also very interesting. The use of SAMP and RAMP hydrazones as well as the 1,3-dioxin method were pioneered by Enders who described several elegant synthetic applications.[9] (Figure 1.3)

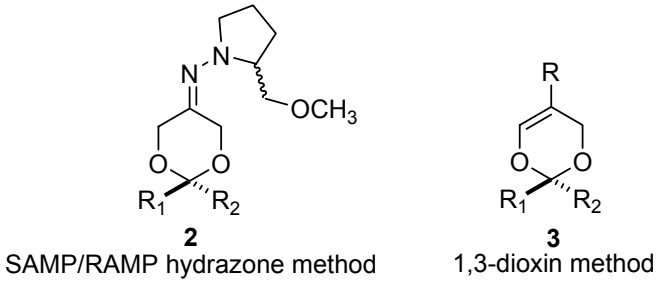


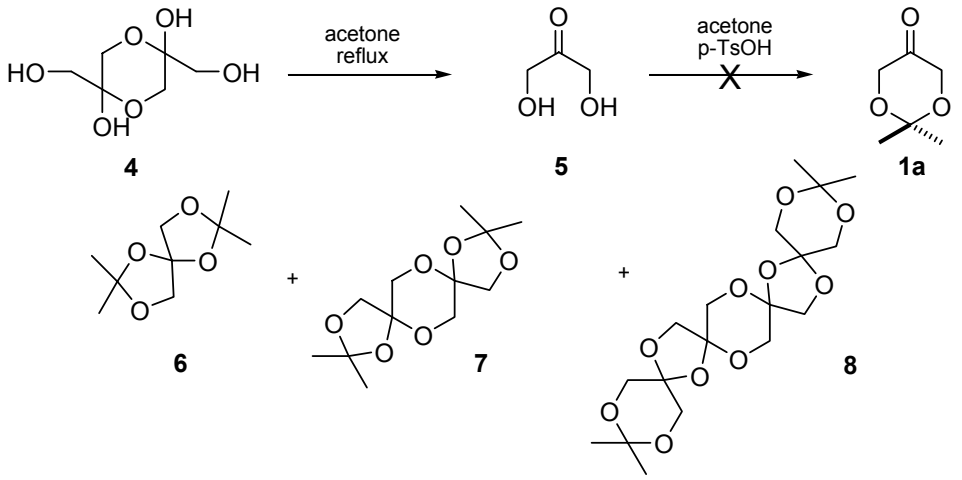

**Figure 1.3** Dioxanone derivatives used in synthesis by Enders.

The literature review will first discuss the work that had been done by our group to put the contents of this thesis into appropriate context. Following that, recent developments in the chemistry of dioxanones worldwide will be briefly reviewed.

## 1.1 Methods of dioxanone synthesis

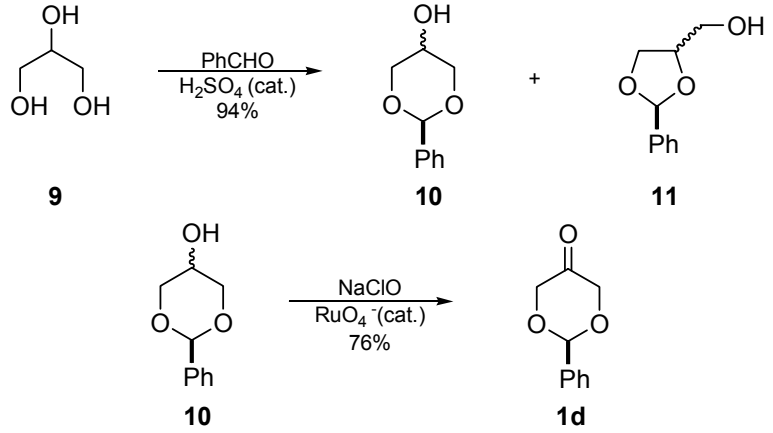
Before exploring the chemistry of dioxanones, the first challenge is to synthesize those staring materials, since they are not commercially available. Possibly the most obvious synthetic route to protected DHA units could be based on a reaction of 1,3-dihydroxyacetone with carbonyl compounds (i.e. acetone for 2,2-dimethyl substituted dioxanone, pinacolone for 2-*tert*-butyl-2-methyl substituted dioxanone and acetophenone for 2-methyl-2-phenyl substituted dioxanone).

This approach was extensively studied by Gleave[10, 11] who observed that in reaction of dihydroxyacetone (obtained from the dihydroxyacetone dimer) with acetone the desired product was not formed, but instead various polymers were obtained (Scheme 1.2).




**Scheme 1.2**

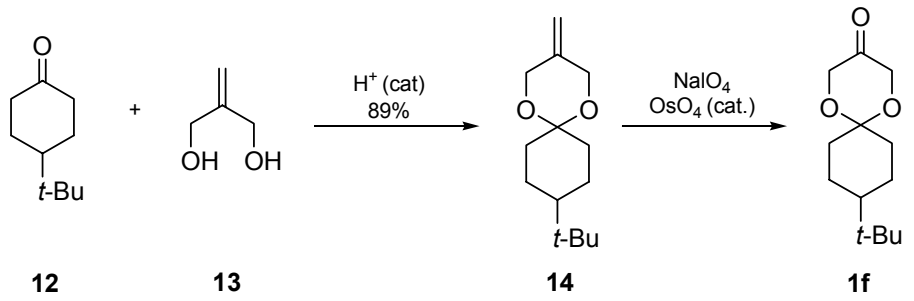
Another approach towards the synthesis of acetal - protected dihydroxyacetone units, presented by Carlsen,[12] was based on the reaction of glycerol (**9**) with benzaldehyde to form the corresponding dioxanol (**10**), which upon oxidation led to the 2-phenyl-1,3-dioxan-5-one (**1d**) (Scheme 1.3).




**Scheme 1.3**

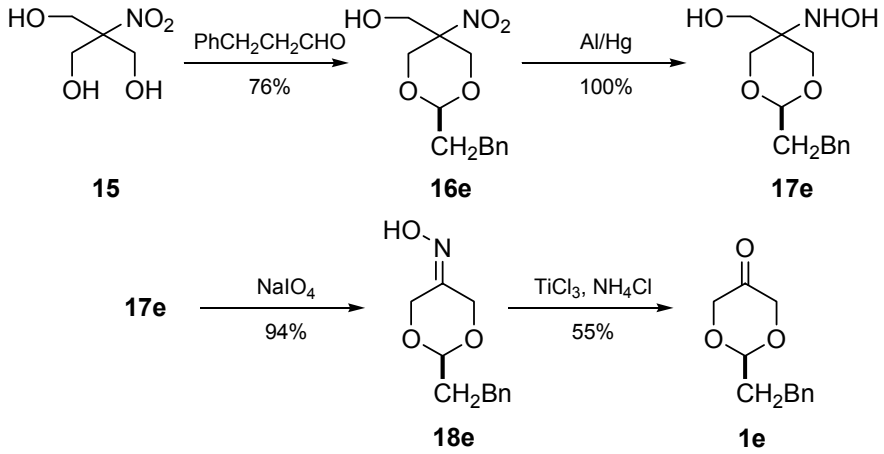
One of the drawbacks of this approach was the formation of two isomeric forms of the protected triol: the expected compound **10** and the undesired product **11** were obtained in almost equimolar ratio. Thus, this synthesis suffered from the low overall yield and lack of atom economy already in the first step.

Corey protocol was based on employing the expensive 2-methylene-1,3-propanediol (**13**) as the ketone building block.[13] Oxidation of the double bond of **14** led to the corresponding dioxanone **1f** in good overall yield (Scheme 1.4).




**Scheme 1.4**

Synthesis of 2-phenethyl-1,3-dioxan-5-one (**1e**) from commercially available tris(hydroxymethyl)nitromethane (**15**) and 3-phenylpropanal was developed by Trost.[14]

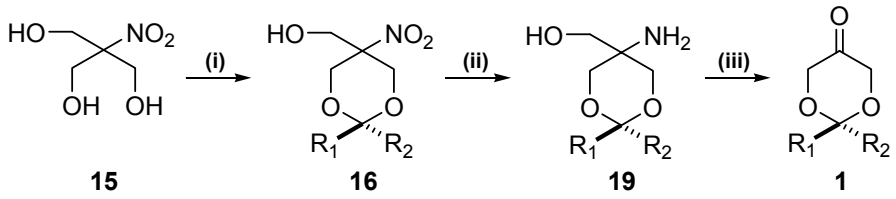



**Scheme 1.5**

It was established that the desired dioxanone **1e** could be formed in the protection/reduction/oxidation/hydrolysis sequence (Scheme 1.5). That protocol was employed in synthesis of various dioxanones by Gleave,[10] however it was found to be poorly reproducible. Especially the yields of the conversion of oximes into the corresponding ketones fluctuated during scaling up (which was the most important issue

from the synthesis point of view).

Nowak[15] investigated the synthesis of dioxanones based on an approach in which the catalytic hydrogenation of the nitro group into the amino group was used. He was able to accomplish the syntheses of several dioxanones of general structure **1** in 40 - 90 % overall yield (Scheme 1.6, Table 1.1, entry 1).




**Scheme 1.6**

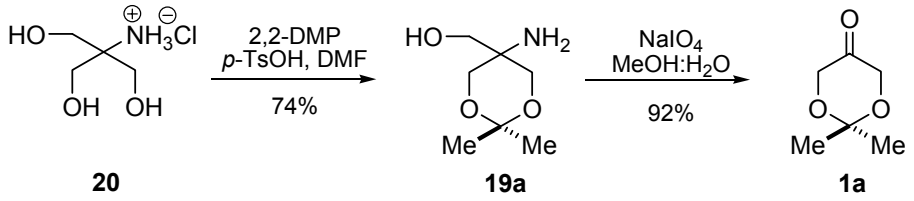
**Table 1.1** Syntheses of dioxanones **1** under different conditions

| Entry | (i) | (ii) | (iii) |
|---|---|---|---|
| 1 | aldehyde/ketone<br>*p*-TsOH, PhH, reflux | $H_2$(1400 psi)/RaNi<br>85°C, EtOH | $NaIO_4$<br>MeOH/$H_2O$ |
| 2 | $(CH_3)_2CO$,<br>$BF_3$•$Et_2O$ | $H_2$/RaNi | $NaIO_4$, $H_2O$ |

This method has been recently modified in our laboratory by changing the conditions of hydrogenation.[16] It was observed that the reaction proceeded well at room temperature, and, moreover, the hydrogen pressure could be reduced from 1400 psi to 50 psi. At the same time longer reaction times were required (from 4 h to 12 h depending on the substrate and on the reaction scale) to obtain the desired product in quantitative yield.

Another approach to dioxanone **1a** ($R_1$=$R_2$=Me) included Lewis acid catalyzed acetalation and catalytic hydrogenation sequence to form β-amino alcohol **19a** which upon cleavage with sodium periodate gave the desired product **1a** in 17 % overall yield (Scheme 1.6, Table 1.1, entry 2).[17]

Even though the 2,2-dimethyl-1,3-dioxan-5-one (**1a**) can be made using the procedures described above, perhaps the simplest and easiest way to obtain this synthetically useful building block is the two step synthesis involving an acid-catalyzed formation of cyclic acetal of the commercially available salt of 2-amino-2-(hydroxymethyl)propane-1,3-diol (**20**) and oxidative cleavage according to the protocol developed by Hoppe (Scheme 1.7).[18]




**20** **19a** **1a**

**Scheme 1.7**

## 1.2 Enolization of dioxanones

Carbon-carbon bond formation is the fundamental process for the construction of the molecular frameworks in organic synthesis. Many carbon–carbon bond forming reactions require interaction between a nucleophilic carbon and an electrophilic one. Two of the most useful moieties that serve as carbon nucleophiles are enolates and enamines. An enolate is a species that is formed upon the removal of the proton from α-carbon atom of a carbonyl compound with a base.[19] Metal enolates are involved in many reactions of carbonyl compounds for example: aldolization, alkylation, halogenation, acylation. The variety of reactions that might be carried on with enolates is shown in Figure 1.4.

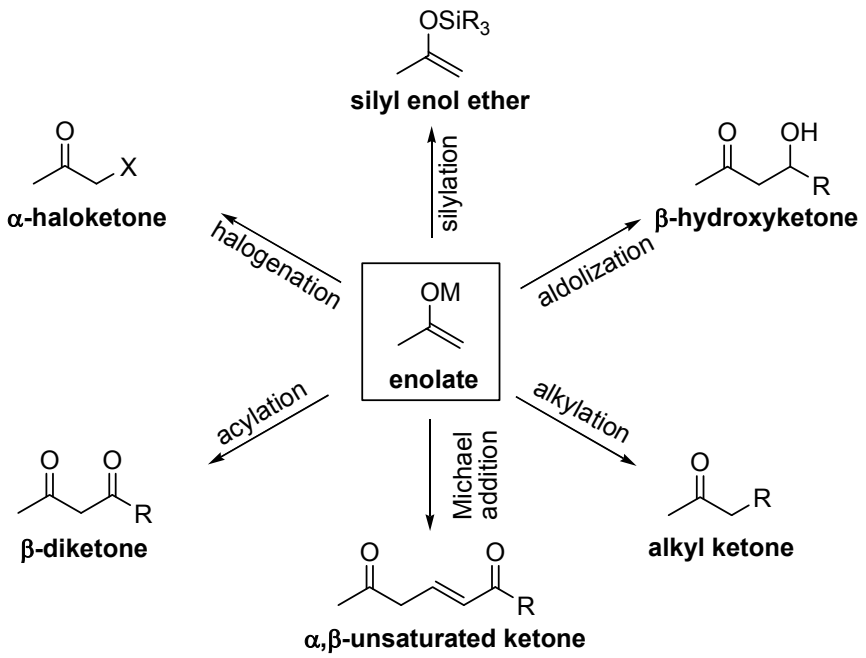
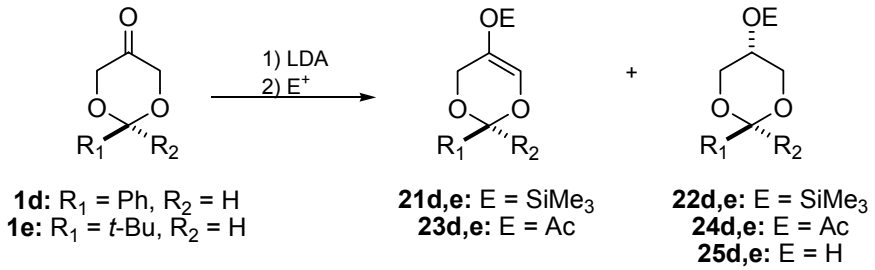



**Figure 1.4** Enolates: major reactions

The most common metals that are associated with the formation of enolates are potassium, sodium, magnesium, boron, tin, titanium, zirconium and lithium (the last being the most popular and versatile).

### 1.2.1 Lithium enolates

Enolization of dioxanones with lithium amide bases was a subject of investigation by Gleave.[10] This objective was found to be relatively difficult to accomplish despite superficial simplicity. Initial studies on the acetal-protected DHA's **1d** and **1e** were not promising. It was observed that deprotonation reaction with LDA, followed by addition of an electrophile (acetic anhydride or chlorotrimethylsilane) gave two products in each case: the expected enol ether/ester **21** or **23** and products which resulted from LDA behaving as the reducing reagent (products **22, 24**). The amounts of reduced products were significant (40 - 65 %) and that clearly indicated the unusual properties of dioxanones which were more agreeable towards reduction (a property characteristic of aldehydes) than deprotonation with LDA (Scheme 1.8).




**1d:** $R_1$ = Ph, $R_2$ = H
**1e:** $R_1$ = *t*-Bu, $R_2$ = H

**21d,e:** E = $SiMe_3$
**23d,e:** E = Ac

**22d,e:** E = $SiMe_3$
**24d,e:** E = Ac
**25d,e:** E = H

**Scheme 1.8**

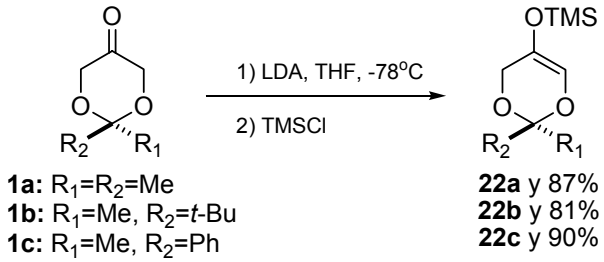
In order to gain insight into the problem, directed aldol reactions were attempted on the enolates of dioxanones **1d** and **1e** using pivalaldehyde or benzaldehyde as the electrophiles. The dioxanols **25d** and **25e** were obtained in 40 – 68 % yield under a variety of conditions (Table 1.2). There was a significant solvent effect and diethyl ether clearly favoured reduction while the reaction in DME was much less clean than in the other solvents and several unidentified side products were detected. It seemed that LDA could be used efficiently for diastereoselective reduction, but not for deprotonation of dioxanones **1d** and **1e**.

**Table 1.2** Reduction of dioxanone **1d** with LDA under different conditions

| Solvent | 25d [%] |
|---|---|
| $Et_2O$ | 81 |
| THF | 63 |
| DME | 64 |

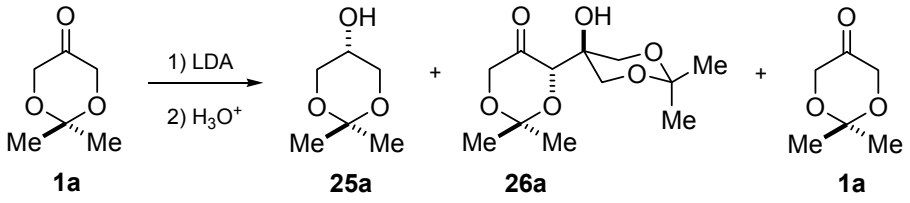
Subsequently, it was found that the reduction could be minimized by using Corey's internal quench procedure for the formation of silyl enol ethers[20] (LDA gave only 5 % of the reduced product of dioxanones **1d** and **1e** under internal quench conditions). Moreover, replacing LDA with lithium amides derived from amines that lack any α-hydrogens (LiTMP or LHMDS) prevented reduction.[21] Thus the reaction of dioxanones with lithium amides could be successfully controlled and, depending on the conditions, either enolization or reduction might be the major pathway. Problem with

the reduction during deprotection process could be solved also by choosing the appropriate dioxanone: the reduction comprised a major problem in the enolization of acetal protected DHA units; on the other hand this pathway was minor in the case of dioxanones derived from ketones. This issue was further investigated by Nowak[15] who observed selective formation of silyl enol ethers as the products in reaction of 2,2-disubstituted-1,3-dioxan-5-ones (**1**) with LDA and trapping corresponding lithium enolates by chlorotrimethylsilane (Scheme 1.9).



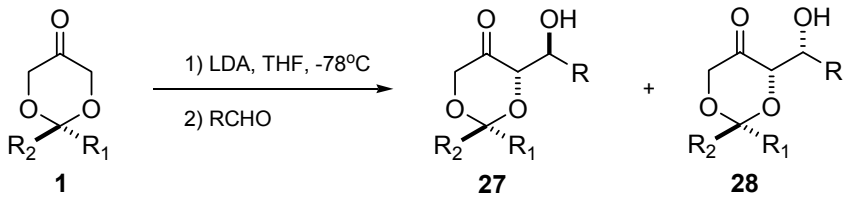

**Scheme 1.9**

Enolization of 2,2-dimethyl-l,3-dioxan-5-one (**1a**) was investigated as well (Scheme 1.10). Deprotonation of **1a** with LDA followed by aqueous quench gave small amounts of the reduction product **25a** (5 % in THF and 17% when $Et_2O$ was used as the solvent) and substantial amounts of the self-aldol product **26a** (up to 64 %).[10] During quench, ketones had been known not to undergo self-aldolization unless they were unusually reactive.[22] Dioxanones, however, are known to be very electrophilic due to the electron withdrawing properties of the α-alkoxy groups, and thus the reactivity of those α-alkoxyketones could be comparable to that of aldehydes.[23]




**Scheme 1.10**

Even thought enolization of 2,2-disubstituted dioxanones might be problematic, surprisingly, the aldol reaction of the lithium enolate of **1** with various aldehydes proceeded well and a mixture of two diastereoisomeric aldol products, *syn* and *anti*, were formed in up to 77 % yield (Scheme 1.11 and Table 1.3).[10, 24]




**Scheme 1.11**

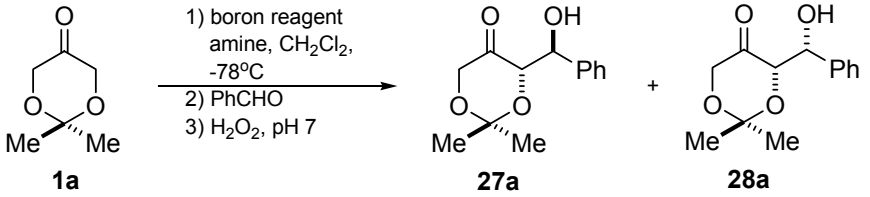
**Table 1.3** Diastereoselectivity in directed aldol reaction of lithium enolates of **1**

| Entry | $R_1$ | $R_2$ | R | 27 : 28 (*anti* : *syn*) | Yield [%] |
|---|---|---|---|---|---|
| 1 | Me | Me | PhCH=CH | 46 : 54 | 44 |
| 2 | Me | Me | *n*-Hx | 62 : 38 | 62 |
| 3 | Me | Me | Chx | 91 : 9 | 61 |
| 4 | Me | Me | Ph | 65 : 35 | 55 |
| 5 | Me | Et | Ph | 65 : 35 | 61 |
| 6 | Me | Ph | Ph | 72 : 28 | 77 |

Reaction of the lithium enolate derived from dimethyl-substituted dioxanone with cinnamaldehyde provided the *syn* and *anti* adducts in almost equimolar ratio (Table 1.3, entry 1). Aliphatic aldehydes, unbranched at the α position, like *n*-hexanal, proved to be less selective (*anti* : *syn* 62 : 38, Table 1.3, entry 2) than cyclohexanecarbaldehyde which gave the *anti* : *syn* ratio of 91 : 9 (Table 1.3, entry 3). The reaction of enolates with benzaldehyde as the electrophile gave modest *anti* selectivities (Table 1.3, entries 4,5) with the exception of 2-methyl-2-phenyl-1,3-dioxan-5-one (**1c**) in which case selectivity and yield were slightly improved (Table 1.3, entry 6). In summary, the lithium mediated aldol reaction was modestly *anti* selective excluding one example of using cyclic, aliphatic aldehyde which demonstrated high *anti* selectivity.

### 1.2.2 Boron enolates

Boron enolates react with aldehydes similarly to lithium enolates, to provide aldol adducts. Due to the differences in the length of metal-oxygen bond (B-O being shorter then Li-O and therefore providing more compact transition state) the selectivities of boron mediated aldol reaction are generally higher than lithium mediated ones.[25] Nowak investigated the aldol reaction of boron enolates derived from 2,2-dimethyl-substituted dioxanone.[24] Summary of those studies is presented in Scheme 1.12 and Table 1.4.



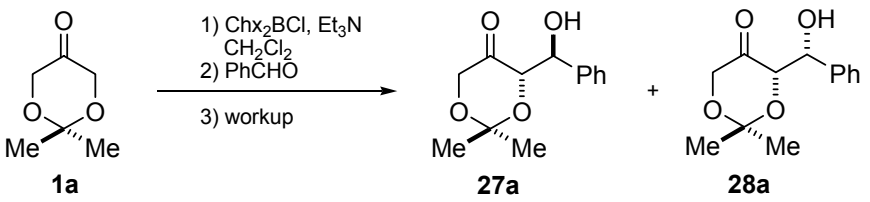

**Scheme 1.12**

**Table 1.4** Diasteroselectivity of boron mediated aldol reaction of **1a**

| Entry | Boron reagent/amine | 27a : 28a (*anti* : *syn*) | Yield [%] |
|---|---|---|---|
| 1 | 9-BBNOTf/DIPEA | 53 : 47 | 51 |
| 2 | $Bu_2BOTf$/DIPEA | 73 : 27 | 46 |
| 3 | $Cp_2BOTf$/DIPEA | 84 : 16 | 47 |
| 4 | $Chx_2BCl/Et_3N$ | 96 : 4 | 64 |

The *anti* selectivity depended on the boron reagent, which was illustrated in the increasing *anti* to *syn* ratio while the steric hindrance of the ligands on boron increased (compare entry 1,2,3 and 4 in Table 1.4). At the same time, isolated yields remained relatively low even though the preliminary studies supported by NMR experiments indicated high conversion. Based on that observation it was concluded that the low yields may be caused by the workup, and as the result several workup conditions were

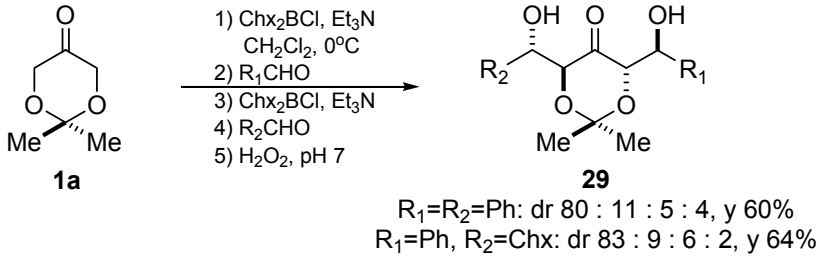
screened (Scheme 1.13).[15]




**Scheme 1.13**

Dimethyldioxirane as well as ozone were found to be the best reagents for oxidative workup in the terms of selectivity (dr > 90) and yield (81 - 83 %). Ethanolamine, sodium perborate and hydrogen peroxide provided moderate to high selectivities of aldol products (from 70 : 30 to 97 : 3 *anti* to *syn*), however lower isolated yields were observed (31 - 73 %).

The potential for using boron enolate chemistry in double aldol reactions was investigated as well. Dimethyl-substituted dioxanone was employed as the model system in a concomitant double-aldol reactions (Scheme 1.14).[26]

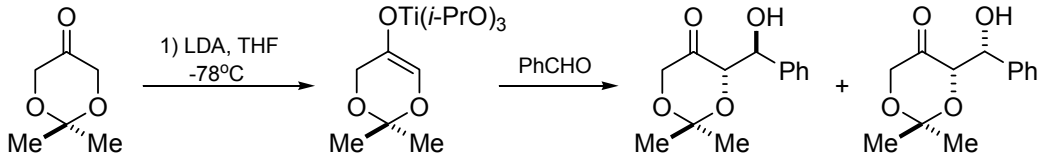



**Scheme 1.14**

The reaction proceeded in highly stereoselective fashion giving, as expected, four diastereoisomers in the 80 : 11 : 5 : 4 ratio when benzaldehyde was used twice in the reaction, and the 83: 9: 6: 2 ratio when first cyclohexylcarbaldehyde and then benzaldehyde were used as the electrophiles. At the same time yields of the reactions remained moderate (ca 60 %).

### 1.2.3 Titanium enolates

The question of obtaining *syn* diastereoselectivity in the aldol reaction of dioxanones was also briefly investigated by Nowak.[15] Unlike lithium or boron mediated reactions of E-enolates that lead to the *anti* isomers predominantly (as rationalized by the Zimmerman-Traxler chair-like transition state),[27] titanium compounds often provide *syn* isomers as the major products. In Nowak's study the titanium enolate was generated *via* a transmetalation process from the lithium enolate, and was then trapped with aldehydes to form aldol adducts (Scheme 1.15).




**1a** **2) ($i$-PrO)$_3$TiCl (eq)** **30** **27a** **28a**

| | | | | |
|---|---|---|---|---|
| 0 | y 55 % | 65 | : | 35 |
| 1 | y 46 % | 45 | : | 55 |
| 3 | y 30 % | 25 | : | 75 |

**Scheme 1.15**

Transmetalation with one equivalent of the titanium reagent provided diastereomeric aldol adducts in nearly equimolar ratio. The aldol product was formed in the *syn* selective fashion only after addition of an excess of the titanium compound, unfortunately the yield of the reaction dropped significantly at the same time. That phenomenon was caused by trisisopropyltitanium (IV) chloride acting not only as the source of Ti for replacing lithium and forming titanium enolate, but also being a relatively strong Lewis acid capable of opening of the acetal ring and causing degradation of the dioxanone system.

### 1.2.4 Enantioselective deprotonation

Development of efficient asymmetric transformations is one of the major goals in organic synthesis. In addition to diastereoselective syntheses many of which have already been developed with high efficiency, enantioselective methods are gaining a lot of attention. In particular enantiodifferentiating transfer of protons is of interest, since the process might provide elegant routes for conversion of symmetrical intermediates into optically active compounds.[28]

Enantioselective deprotonation using chiral lithium amide bases represents an attractive and powerful method in asymmetric synthesis.[29] A number of strategies have been described that demonstrate the ability and application of such bases in targeted syntheses to provide compounds with high enantiomeric excess (ee). Over the years several efforts to develop the "perfect" chiral base were described,[29] and these studies had provided versatility of reagents with different chiral moieties attached to nitrogen. In our laboratory a variety of chiral lithium amide bases were prepared with intent to apply them in methodological studies[30-32] and in natural products synthesis.[33-37] Some of them are shown in Figure 1.5

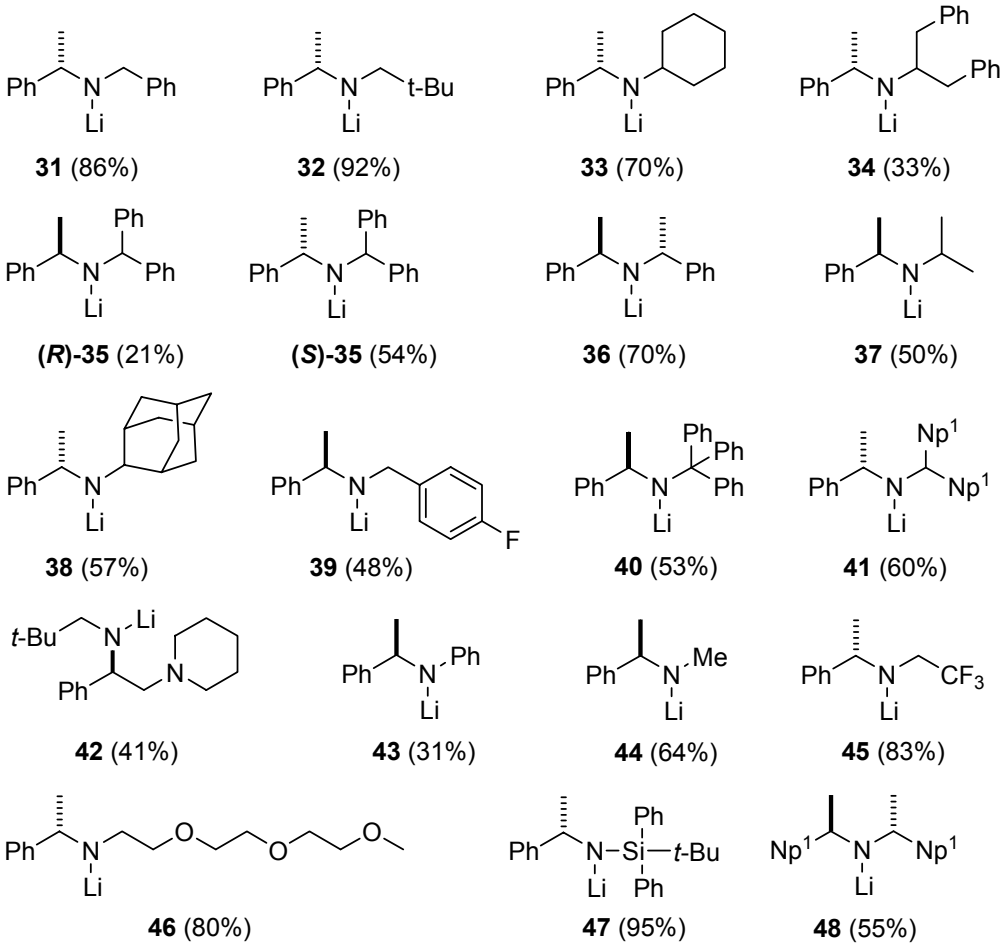
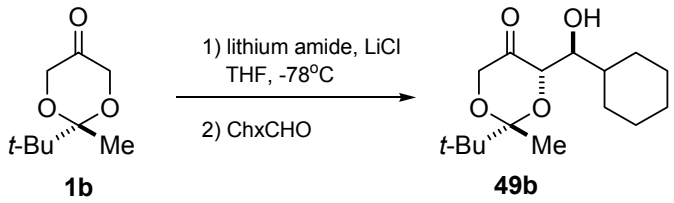



**Figure 1.5** Chiral lithium amides synthesized in our laboratories

Enantioselective deprotonation of acetal protected dioxanones with chiral lithium amides was first investigated by Gleave[10] and the studies were continued by Nowak.[15] In the early studies it was observed that enantioselectivities in the aldol reaction of **1b** with cyclohexanecarbaldehyde were relatively low. The highest value of 60 % ee was observed when lithium amide **(*R*)-35** was used in the deprotonation step and yields varied from 32 to 58 %. In the light of those results the obvious question arose: whether the structure of amide and the presence of additive might affect enantioselectivity or not?

In the studies on deprotonation of **1b** with chiral lithium amides derived from α-methylbenzylamine the correlation of the selectivity (ee) with the steric bulk and the presence of aromatic groups in the amide skeleton was postulated. Moreover, an

investigation done by Lazny[32] on tropinone and Nowak[32] on dioxanones have shown a relationship between the amount of LiCl and enantioselectivity in aldol reactions mediated by chiral lithium bases. Following up on literature precedents[38-40] and on studies from our laboratory[21, 41] experiments were done in the presence of 1.0 equivalent of LiCl. Summary of these studies are depicted in Scheme 1.16 and Table 1.5.




**Scheme 1.16**

**Table 1.5** Enantioselective aldol reaction of **1b** with cyclohexylcarbaldehyde in the presence of 1.0 eq of LiCl

| Entry | Chiral base | ee [%] | Yield [%] |
|---|---|---|---|
| 1 | **(*S*)-35** | 72 (+) | 48 |
| | | 70 (+)[a] | 60 |
| 2 | **34** | 60(+) | 76 |
| 3 | **41** | 90 (+) | 95 |
| 4 | **32** | 19 (+)[b] | 63 |
| 5 | **38** | 80 (+) | 91 |
| 6 | **47** | - | - |
| 7 | **46** | 2 (+)[c] | 66 |
| 8 | **45** | 90 (+) | 61 |
| | | 87 (+) | 86 |

[a] Reaction performed at -100 °C. [b] The chiral lithium amide was generated from amine hydrochloride [c] TMS enol ether was used as an equivalent of dioxanone.

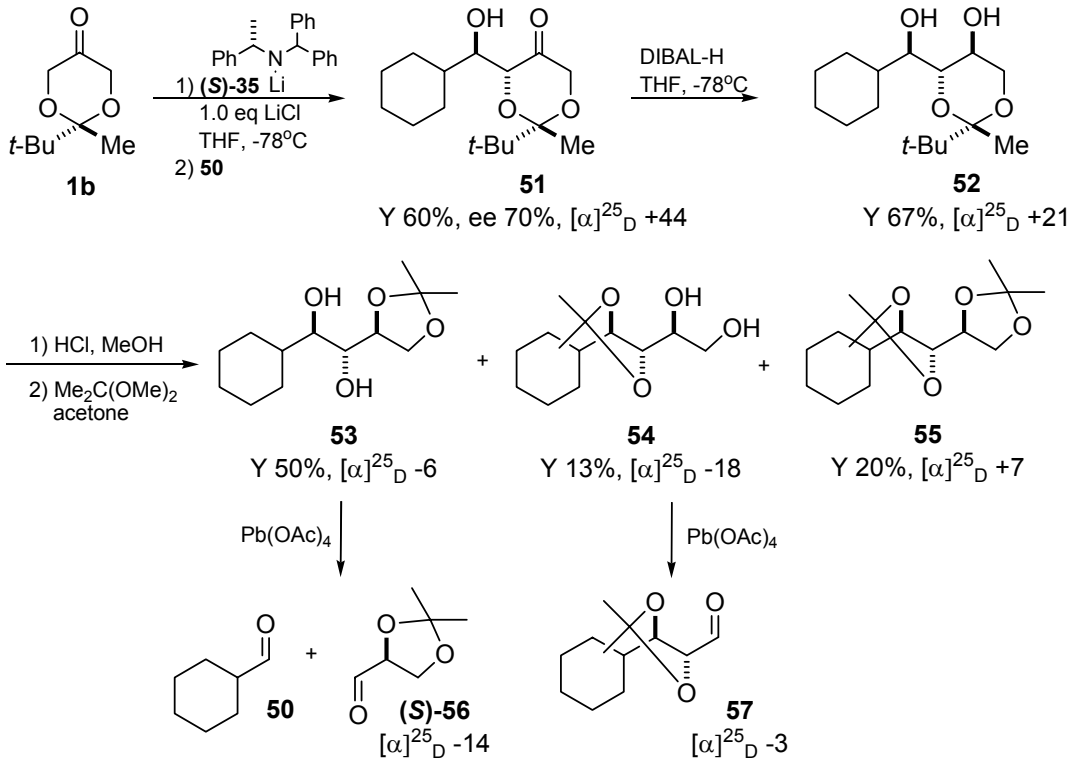
Lithium amide (***S*)-35** gave moderate ee even after lowering the temperature to -100 °C (Table 1.5, entry 1). Substitution of the phenyl groups with 1-naphthyl in the amide

structure was responsible for increase of the ee of the product which was formed in 95 % yield (Table 1.5, entry 3). The amide with the large neopentyl substituent gave only 19 % ee, on the other hand bulky adamantyl attached to the nitrogen provided the desired product with 80 % ee (Table 1.5, entries 4,5). The amide **47** having a large substituent was unable to deprotonate dioxanone (Table 1.5, entry 6). Mixture of isomers that were difficult to separate was obtained when lithium amide **46** was used. Aldol reaction was then performed via the corresponding silyl enol ether; however the resulting product was practically racemic (Table 1.5, entry 7). The trifluoroethylamide **45** was a very selective deprotonation reagent giving the ee's up to 90 %. Another advantage of using this amide, that had been originally developed by Koga,[42] is the simplicity and cost of its synthesis, which has to be taken under consideration while planning experiments on a large scale.

### 1.2.5 Absolute stereochemistry of deprotonation of dioxanones

The next question regarded absolute stereochemistry of the products. This problem was addressed by Nowak who proposed an indirect but elegant route for establishing the stereochemical preferences of chiral lithium amides in enantioselective deprotonation of dioxanones (Scheme 1.17).[26]

The aldol addition of the enolate derived from the reaction of the parent ketone **1b** with the chiral lithium amide (***S***)**-35** afforded the adol product **51** in 70 % ee. Reduction of **51** with diisobutylaluminum hydride (DIBAL-H) gave two diastereoisomeric diols in a ratio of 92 : 8. The major product, diol **52,** was isolated in 67 % yield. The minor product was crystalline and provided well-defined crystals that were subjected to X-ray crystallography which provided the evidence of the relative stereochemistry. Acid catalyzed hydrolysis followed by transacetalation led to the formation of three products **53, 54** and **55.** Compound **53** was cleaved readily with lead tetracetate to give protected (*S*)-glyceraldehyde (***S***)**-56**.




**Scheme 1.17**

Based on this study, it was postulated that chiral lithium amides obtained from (*S*)-α-methylbenzylamine abstract selectively the pro-*S* proton in the dioxanone molecule and the amides that are derived from (*R*)-α-methylbenzylamine preferentially abstract the pro-*R* proton.[15]

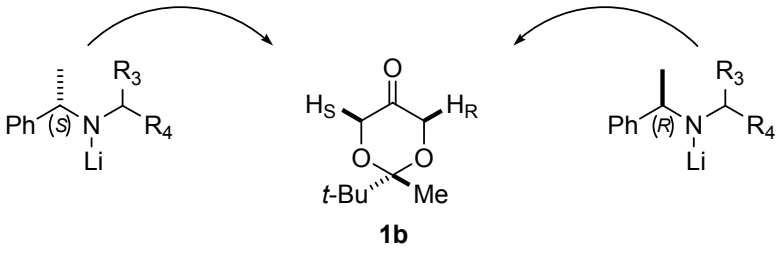


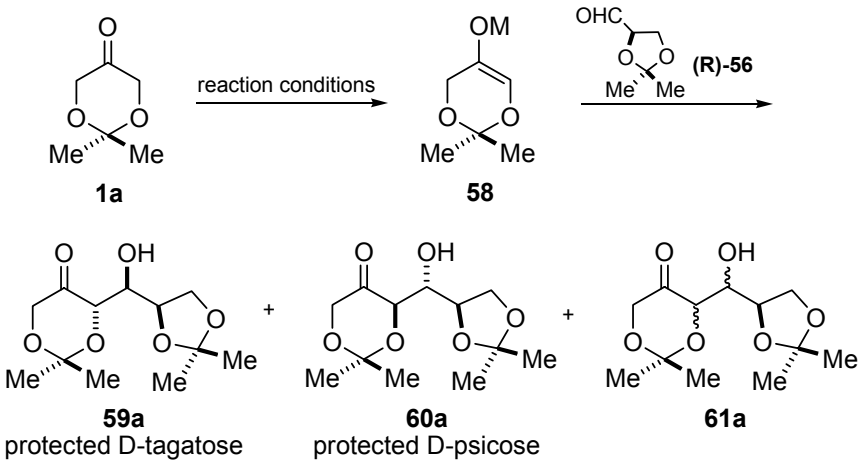

**Figure 1.6** Stereochemical preferences of chiral lithium amides in deprotonation of **1b**

## 1.3 Aldol reactions: application to synthesis of carbohydrates

In the foregoing sections the development of conditions for high diastereoselectivity using boron enolates and high enantioselectivity using lithium enolates was presented. It had been demonstrated that a dioxanone could be deprotonated in an enantioselective fashion leading to the desired product with ee of up to 90 % with the proper choice of the chiral base. Next, this dioxanone-based methodology was successfully applied in the synthesis of carbohydrates.

Although the main topics in modern carbohydrate synthesis are associated with manipulation of readily available monosaccharides and synthesis of oligosaccharides, stereoselective total synthesis of rare sugars is a challenging and practically important task. Worth mentioning is a fact that chemistry of ketohexoses is much less developed then that of aldohexoses and therefore it is even more attractive from the diversity space point of view.

Carbohydrate synthesis via a simple aldol reaction was first investigated by Gleave[10] who reacted 2,2-dimethyl-1,3-dioxan-5-one (**1a**) with its isomeric form - protected (*R*)-glyceraldehyde (***R*)-56.** Three out of four possible isomers were formed in good overall yield, however the selectivity of the reaction was relatively low (Scheme 1.18, Table 1.6, entry 1) and the major components of the product mixture were tentatively assigned as protected D-tagatose (**59a**) and protected D-psicose (**60a**).



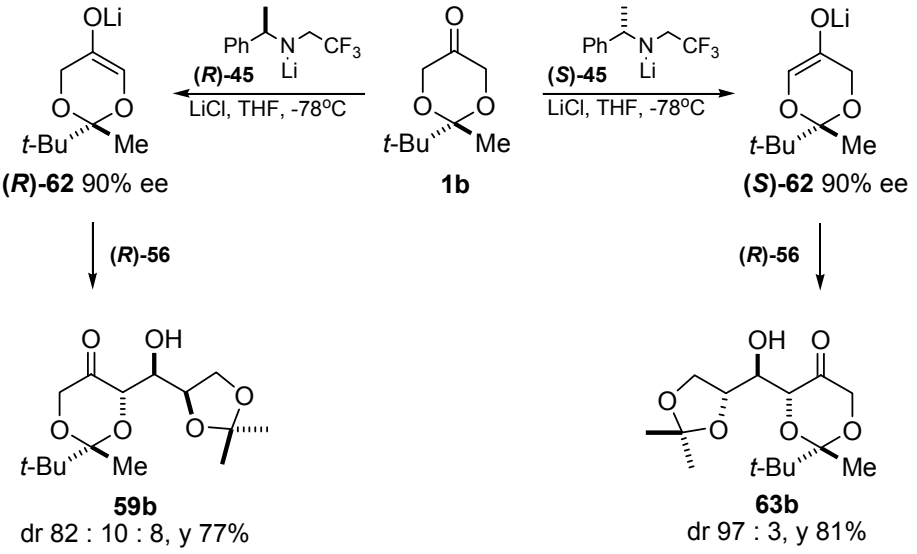

**Scheme 1.18**

**Table 1.6** Selectivity in aldol reaction of dioxanone **1a** and protected (*R*)-glyceraldehyde under different reaction conditions

| Entry | Reaction conditions | Aldehyde | Products ratio 59a : 60a : 61a | Isolated yield [%] |
|---|---|---|---|---|
| 1 | LDA, THF, -78°C | $R_1 = R_2 = Me$ | 55 : 33 : 12 | 70 |
| 2 | $Chx_2BCl$, $Et_3N$, $CH_2Cl_2$, -78°C $H_2O_2$, pH7 | $R_1 = R_2 = Me$ | 85 : 15 : 0 | 39 |
| 3 | $Chx_2BCl$, $Et_3N$, $CH_2Cl_2$, -78°C DDO | $R_1 = R_2 = Me$ | 85 : 15 : 0 | 59 |

In order to make this reaction more useful from the synthetic point of view, boron enolate chemistry was explored as it had already proven to give higher selectivieties.[25] A dicyclohexylborane-mediated aldol reactions performed with higher selectivity than that of lithium enolate albeit changing the work-up conditions was necessary for obtaining better yields (Table 1.6, entry 2, 3).

Employing the well established enantioselective deprotonation in the reaction of chiral enolate of dioxanone and chiral aldehyde gave the opportunity for matched or mismatched processes resulting from double stereodifferentiation.[43]

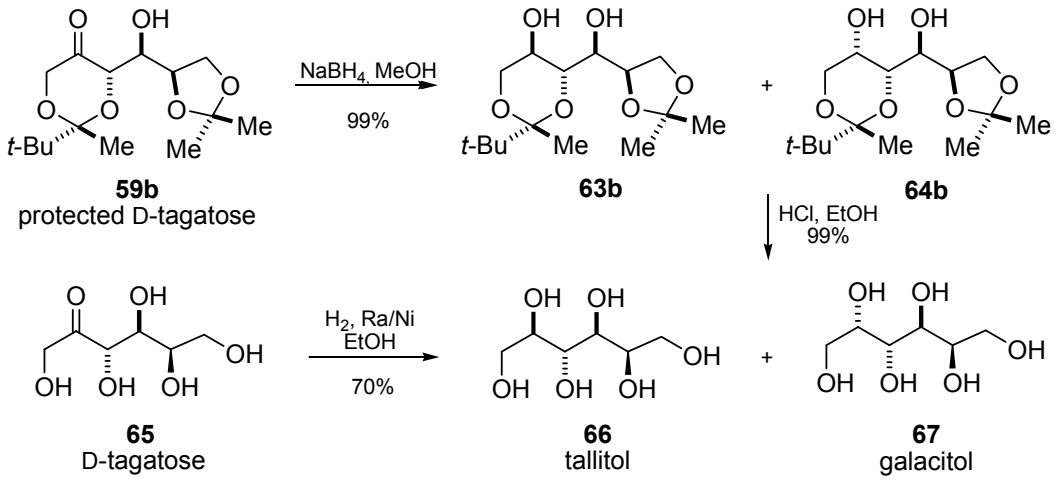



**Scheme 1.19**

Accordingly, the two enantiomeric enolates (***R***)**-62** and (***S***)**-62** were generated (Scheme 1.19) and successfully applied in the reaction with protected glyceraldehyde (***R***)**-56**. The yields were high in all cases (77 – 81 %). Selectivity in each of the examples was moderate to good with the special recognition of isopropylidene protected glyceraldehyde that reacted in highly selective fashion. The double stereodifferentiation effect, significant in each of the presented examples, might be associated with tendency of glyceraldehyde to demonstrate core facial preference and leading the chiral enolate of dioxanone to play irrelevant role in stereoselective outcome in this reaction.

### 1.3.1 Assignments of stereochemistry of carbohydrates

During the synthesis of any natural product an important consideration is the assignment of relative and/or absolute stereochemistry. That was also the case in solving of the structure of the newly synthesized hexoses, which had proven to be a non-trivial task.[15] Eventually the assignment of the relative and the absolute configuration was accomplished by the chemical correlation method. The aldol products were reduced with sodium borohydride to the corresponding protected hexitols. Next the protecting groups were removed by acid-catalyzed hydrolysis and the products were compared with the reduced samples of the commercially available six-carbon sugars. A schematic summary of these studies is shown in Scheme 1.20




**Scheme 1.20**

## 1.4 Dioxanones in organocatalysis

In the following paragraph I will introduce the organocatalytic achievements in the chemistry of dioxanones. The area of organocatalysis is growing very rapidly which is represented by an increasing number of publications each year (Figure 1.7). As it is rather impossible to illustrate all the accomplishments in this topic, since there are many reviews,[44-46] and books[47-50] on that subject, I concentrated mostly on the major undertakings which are related to the chemistry of dioxanones.

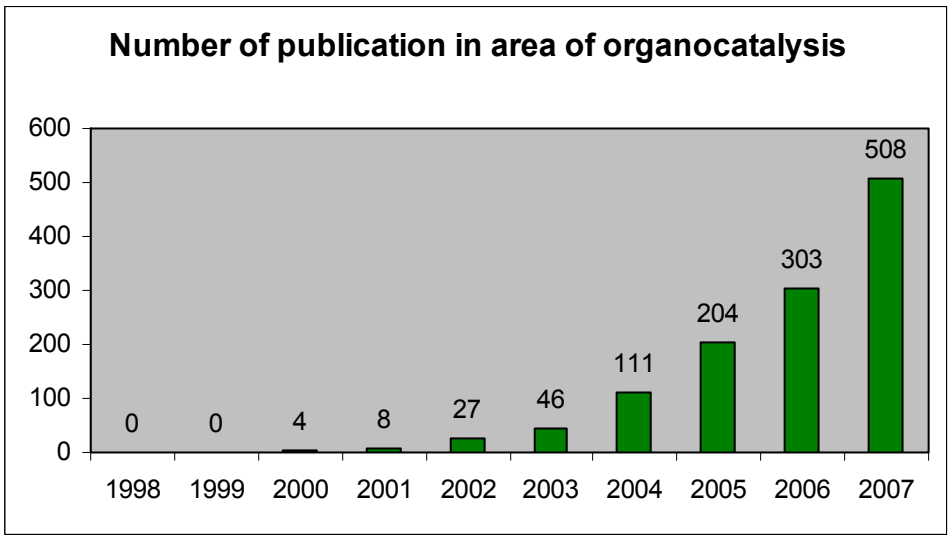


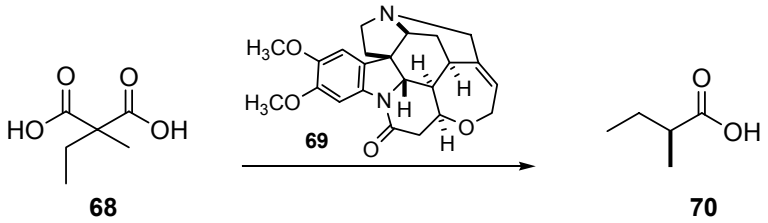

**Figure 1.7** SciFinder hits related to works published on organocatalysis

### 1.4.1 Organocatalysis

Organocatalysis refers to a form of catalysis, whereby the rate of a chemical reaction is increased by an "organic catalyst" consisting of carbon, hydrogen, sulfur and other non-metal elements found in organic compounds. A word catalysis was suggested in 1835 by Berzelius[51] and was related to a process whereby the rate of a particular chemical reaction was hastened, sometimes enormously so, by the presence of a substance which did not itself seemed to take part in the reaction. The term "organic catalysts" was introduced in order to distinguish small organic molecules as catalytic principles from enzymes or inorganic catalysts. MacMillan rediscovered

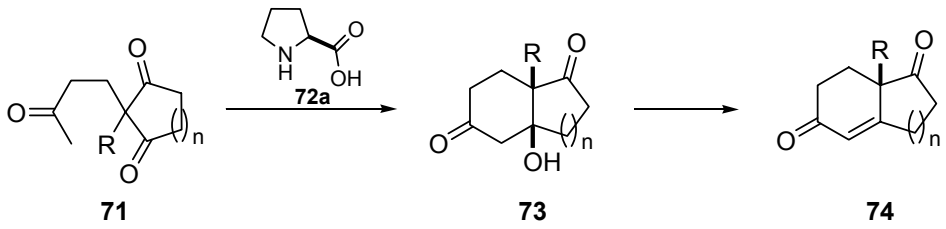
"organocatalysis" and proposed the name in 2000[52] as the dictum for this field of research and it has been used in the literature since then.

In 1904 Marckwald performed enantiotopic group selective decarboxylation of malonic acid derivative **68** in the presence of brucine (**69**) as a catalyst which gave valeric acid (**70**) in 10 % enantiomeric excess (Scheme 1.21).[53]




**Scheme 1.21**

Even though this reaction was one of the first examples of using an organic catalyst in an enantioselective chemical transformation, (*S*)-proline (**72a**) catalyzed Robinson annulation, independently discovered by two groups at Schering[54] and at Hoffmann-La Roche,[55] commonly called the Hajos-Parrish-Eder-Sauer-Wiechert reaction, is viewed as the established literature example of organocatalysis and is known as the fundamental event in the history of organocatalytic processes (Scheme 1.22).




**Scheme 1.22**

Proline, the simplest enzyme model, known also as non-demanding reaction conditions catalyst formed a foundation in the field of organocatalysis. This non-metallic, small-molecule is nontoxic, inexpensive, and commercially available in both enantiomeric

forms. The reactions catalyzed by proline do not require inert atmosphere conditions and could be run at room temperature, potentially even on an industrial scale. Moreover, prior modification of the carbonyl substrates such as deprotonation or silylation is not necessary. Its stability (in comparison to metal based catalysts), easy access and properties allowing for possibility of removal from the reaction mixture by a simple aqueous extraction are only a few advantages responsible for the fact that this amino acid has been used as a catalyst in a wide range of asymmetric transformations with excellent results.

Since the first use of this molecule,[56, 57] numerous organocatalytic systems were developed, allowing extraordinary levels of efficiency, widening the scope of substrates and possibilities in application in target oriented syntheses. In the course of these investigations several modifications were made to defeat the initial drawbacks, such as long reaction times, high catalyst loading or excess of reagents and thus to improve the potential for use of this powerful method in large scale synthesis. All these achievements would not have been possible without an understanding of the mechanism involved (Figure 1.8).[57, 58]

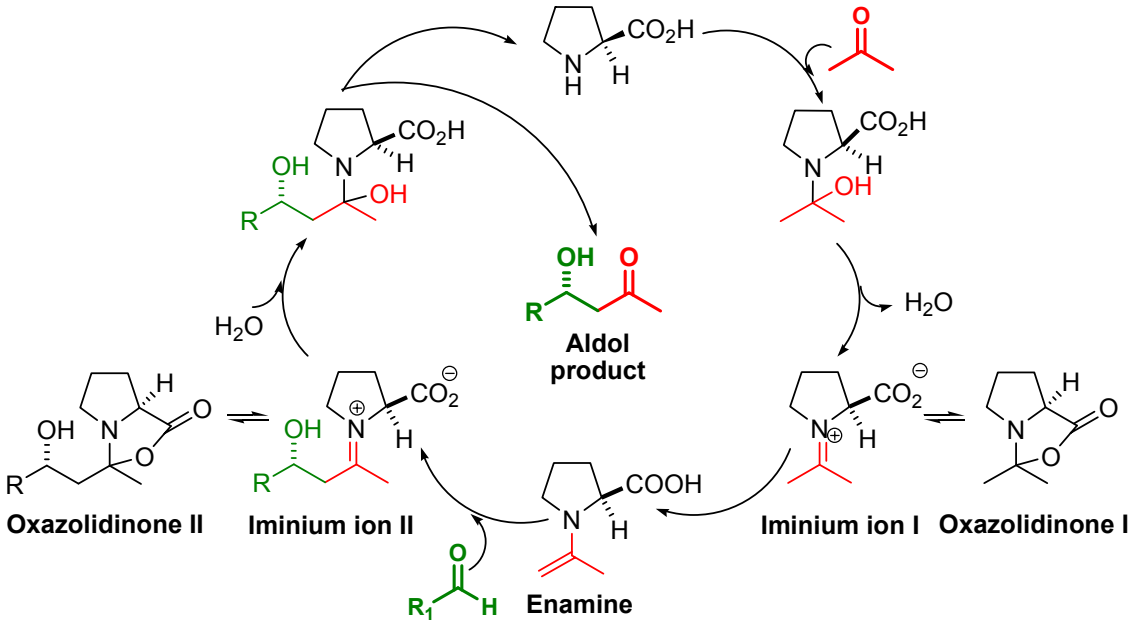



**Figure 1.8** Catalytic cycle in (*S*)-proline catalyzed aldol reactions

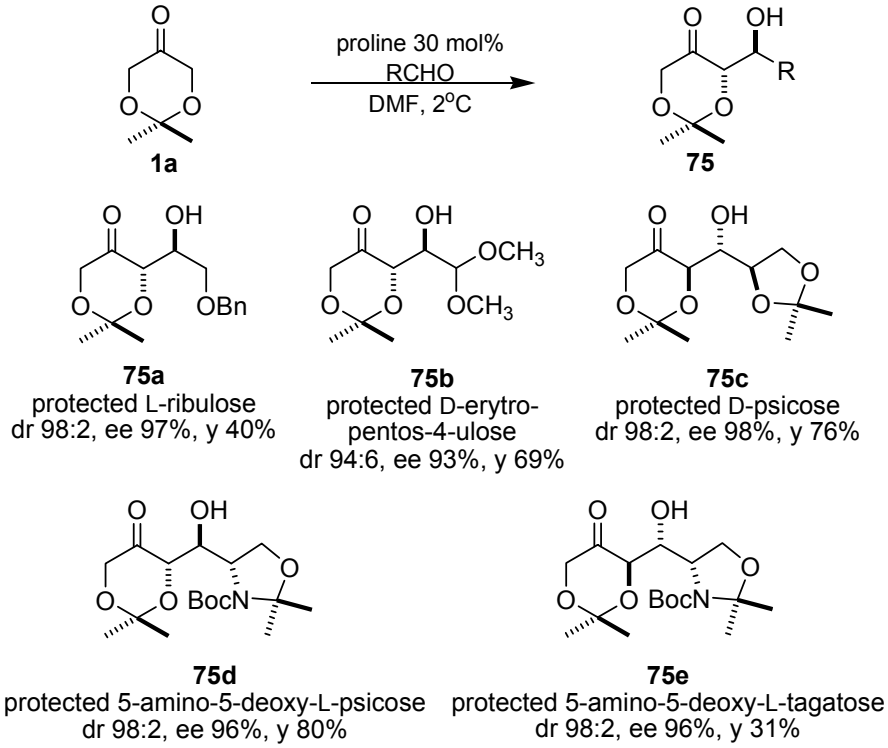
In the catalytic cycle outlined in Figure 1.8 the chiral secondary amine (proline) is presented as a "micro-aldolase" that provides both the nucleophilic amino group and an acid/base co-catalyst in the form of the carboxylate. This co-catalyst perhaps facilitates each individual step of the mechanism, including the nucleophilic attack of the amino group, the dehydration of the carbinol amine intermediate, the deprotonation of the iminium species, the carbon-carbon bond forming step, and both steps of the hydrolysis of the iminium-aldol intermediate. The catalysts, proline in this case, forms the corresponding iminium ion with the ketone. This intermediate reacts by the imine–enamine tautomerism (or a related mechanism) to form the nucleophilic enamine species, which is trapped conveniently by a reactive electrophile (aldehyde).

The acquired knowledge in this area allowed the applications of this strategy to the methodological studies and consequently to synthesis of natural products.

### 1.4.2 Aldol reactions of dioxanones under organocatalytic conditions

Since the pioneering work of List and Barbas,[56] an expansion of the enantioselective proline catalyzed aldol has begun. As an example, aldol reactions between aldehydes and disubstituted dioxanones, useful building blocks, have been developed by several groups, providing a biomimetic asymmetric synthesis of various carbohydrate scaffolds in a fashion analogous to aldolase enzymes (see the Results and Discussion chapter).[59-64]

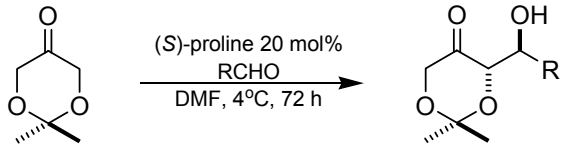
Enders investigated aldol reaction of dioxanone catalyzed by (*S*)-proline with an aim of synthesis of carbohydrates (Scheme 1.23).[59]




**Scheme 1.23**

Stereoselective synthesis of simple protected ketose derivatives **75a** and **75b,** aminosugars **75d** and **75e** and ketoses **75c** was accomplished, thus expanding the earlier studies by Nowak that involved a different protocol, as described previously.[24] Organocatalysis provided a simpler, direct approach to differently protected carbohydrates practically in one step, with high selectivities (de 88 – 96 %, ee 93 – 98 %).

Barbas and co-workers investigated the aldol reaction of **1a** with aliphatic acceptors (Scheme 1.24).[64]

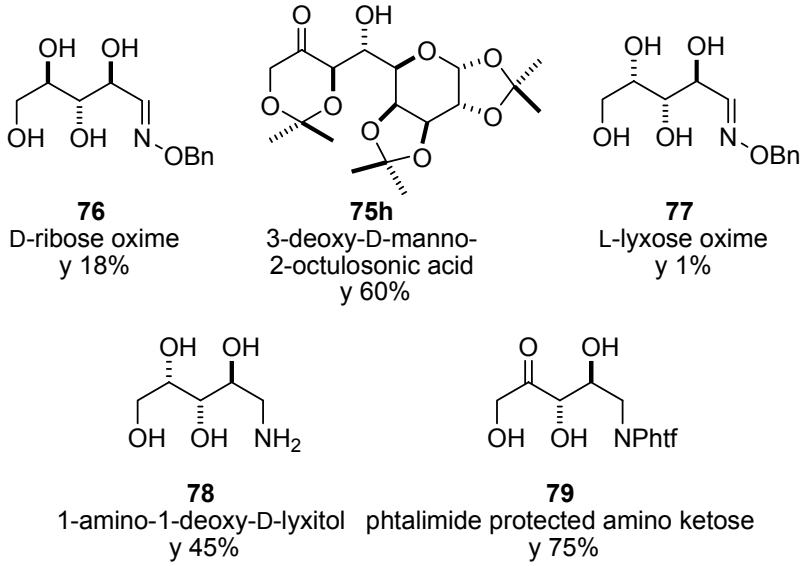



**1a** **75**

**75b:** R=$CH_2$Phtf, dr 18:1, ee 98%, y 60%
**75f:** R=$CH_2$OAc,dr >15:1, ee 98%, y 60%
**75g:** R=$CH_2$Phtf, dr 55:1, ee 98%, y 75%

**Scheme 1.24**

The aldol products were obtained with excellent diastereo- and enantioselectivities albeit in moderate yields (60 – 75 %). This strategy was applied in synthesis of pentose derivatives, aminosugars and higher carbohydrates. Selected examples are depicted in Figure 1.9.



**76**
D-ribose oxime
y 18%

**75h**
3-deoxy-D-manno-
2-octulosonic acid
y 60%

**77**
L-lyxose oxime
y 1%

**78**
1-amino-1-deoxy-D-lyxitol
y 45%

**79**
phtalimide protected amino ketose
y 75%

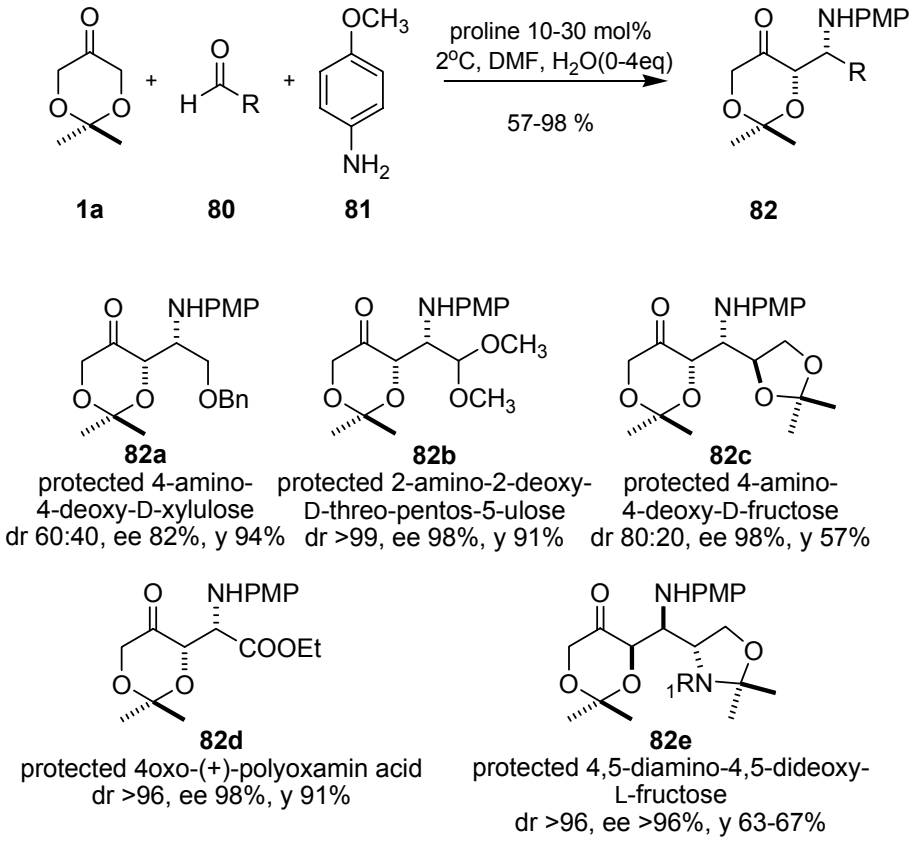
**Figure 1.9** Selected examples of sugar derivatives synthesized by Barbas's group.

After the proline catalyzed aldol reaction found application in synthesis of carbohydrates, researchers started to apply this methodology in other types of reaction.

### 1.4.3 Mannich reactions of dioxanones under organocatalytic conditions

The Mannich reaction is a useful transformation to access amine-containing targets. For many years researchers were trying to overcome the disadvantages of the classic Mannich reaction which are related to the lack of stereocontrol and the formation of by-products. After successes in organocatalytic aldol reaction, several groups started to apply this methodology to Mannich chemistry. As the result, development of the more selective and, in particular, diastereo- and enantioselective protocols for this important C-C bond-forming reaction has been reported.[64]

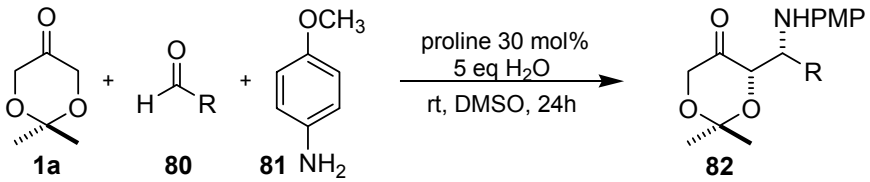
An one-pot, three-component Mannich reaction was investigated by Enders with the aim of synthesis of aminosugars (Scheme 1.25).[65]




**Scheme 1.25**

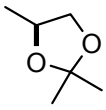
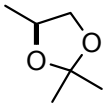
Synthesis of several, protected aminosugars was accomplished in a multicomponent Mannich reaction starting from simple and commercially available compounds. The presence of an organic catalyst (proline or proline derivatives[66]) lead to the formation of the β-amino products with good selectivities (dr 60 – 99 %, ee 82 – 98 %) and yields up to 94 %.[67]

In a similar study, Cordova investigated the conditions for the efficient Mannich reaction (Scheme 1.26, Table 1.7).[68]




**Scheme 1.26**

**Table 1.7** Proline catalyzed Mannich reaction of **1a**

| Entry | R | Yield [%] | dr *syn* : *anti* | ee [%] |
|---|---|---|---|---|
| 1 | H | 84 | | >99 |
| 2 | -$CO_2$Et | 77 | 16:1 | >99 |
| 3 | Bn$OCH_2$- | 70 | 6:1 | 98 |
| 4 |  | 40 | 3:1 | 98 |
| 5[a] |  | 55 | >19:1 | 98 |
| 6 | -*i*-Pr | 60 | 4:1 | 48 |
| 7 | -Ph | 80 | 3:1 | 76 |

[a](*R*)-proline used in the reaction

It was established that the reactions proceeded with excellent chemoselectivity leading to the corresponding amino sugars in moderate yields (40 – 84 %). Selectivity (*syn* : *anti*) depended on the substrate and varied from 3 : 1 (entry 4 and 7) to 16 : 1 (entry 2). Significant facial selectivity was observed in the case of protected (*R*)-glyceraldehyde that reacted in highly selective fashion when (*R*)-proline was used as the catalyst (compare entries 4 and 5).

The *anti* selectivity of the (*S*)-proline-catalyzed aldol reaction referred to *re*-facial attack on the aldehyde by the *si*-face of the enamine (Figure 1.10 IIIa, IIIb). On the other hand, in (*S*)-proline-catalyzed Mannich reactions, the *si*-face of the imine reacted with the *si*-face of the enamine (Figure 1.10, IIa, IIb) leading to the *syn* product being major. The switch of facial selectivity between the aldehyde and the imine could be explained by the fact that a *re*-facial attack on the imine would have resulted in an unfavourable steric interactions between the pyrrolidine ring and aromatic ring (Fig. 1.10).

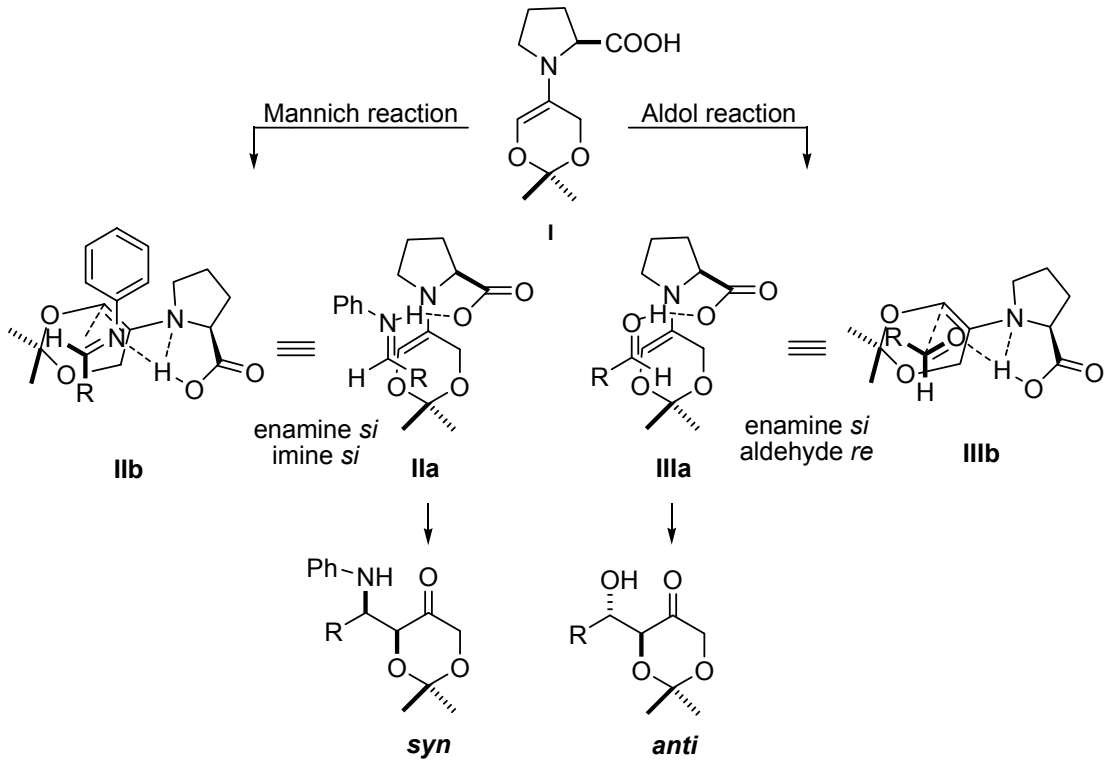
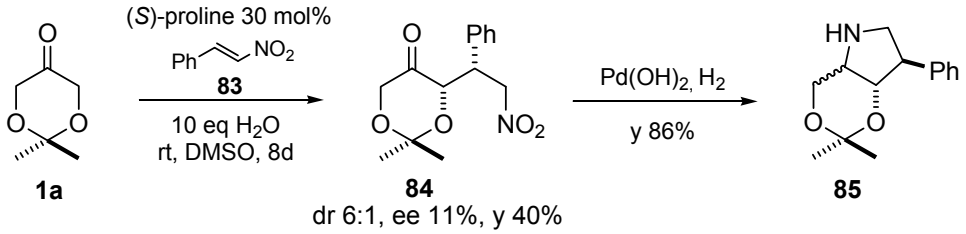



**Figure 1.10** Selectivity in (*S*)-proline catalyzed aldol and Mannich reactions.

### 1.4.4 Miscellaneous reactions of dioxanones under organocatalytic conditions

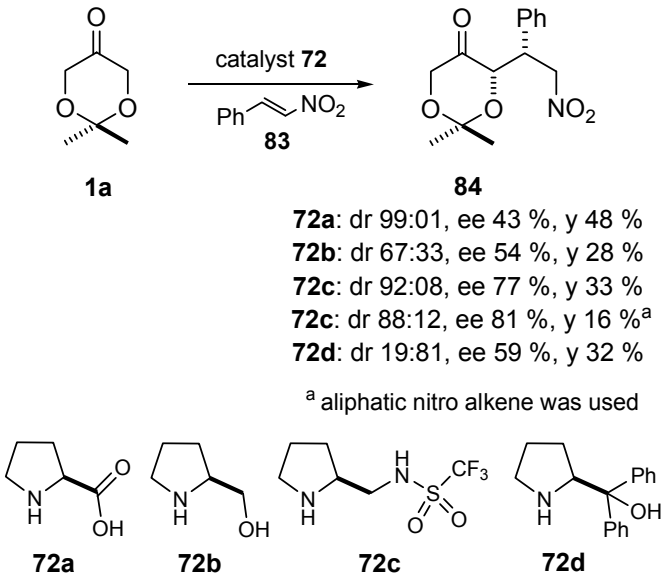
#### a) The Michael reaction

The stereoselective conjugate addition of carbon nucleophiles to electron-poor alkenes is one of the important transformations in modern synthetic chemistry. Among these, the Michael reaction deserves special recognition. This process was studied by Cordova in the organocatalytic context.[68] In an original experiment, dioxanone **1a** reacted with phenylnitrostyrene (**83**) in the presence of a catalytic amount of (*S*)-proline and in wet DMSO. The Michael product was isolated in 40 % yield with 6 : 1 dr and 11 % ee, and, upon hydrogenation, yielded pyrrolidine (**85**) in 86 % yield.




**Scheme 1.27**

Enders attempted to optimize reaction conditions towards obtaining the desired Michael product from a dioxanone in the selective fashion (Scheme 1.28).[69] It was demonstrated that excellent *syn* diastereoselectivities and moderate enantioselectivities (81 – 86 %) could be achieved when Wang's[70] catalyst **72c** was used. The addition of water accelerated the conversion and provided a better yield with shorter reaction times. Studies with a Jorgensen type catalyst **72d** gave reversal of diastereoselectivity, favouring the *anti* configuration.

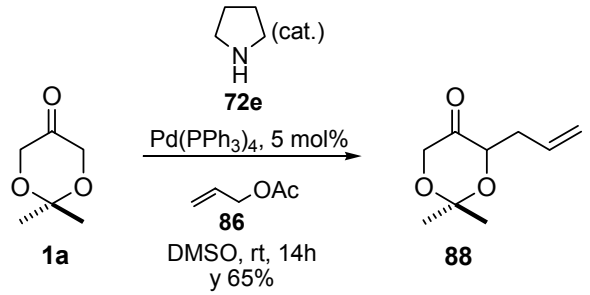



**Scheme 1.28**

**b) Alkylation reaction**

The α-alkylation of carbonyl compounds is an important carbon–carbon bond-forming reaction. Despite a large interest in application of this type of reaction, there is no easy and practically useful protocol for alkylation of dioxanone. All attempts to alkylate dioxanones *via* metal enolates failed. Enders SAMP/RAMP methodology[9] served to provide α-alkylated dioxanones indirectly, however this procedure requires expensive reagents. Alkylation of the lithium enolate of **1a** had been reported only once by Francl,[71] however, despite multiple attempts, it could not be repeated in our group. Instead of the desired product, the dioxanone dimer was isolated as the major product.[15]

In 2006 Cordova proposed a combination of the transition - metal catalysis and organocatalysis as a tool for successful alkylation of dioxanones (Scheme 1.29).[72]




**Scheme 1.29**

Mechanism of the reaction probably involves formation of the enamine intermediate which attacks the electrophilic palladium π-allyl complex generated in situ. Reductive elimination and successive hydrolysis of the iminium intermediate regenerate Pd (0) and pyrrolidine, and yields the α-allylic alkylated dioxanone (Figure 1.11).

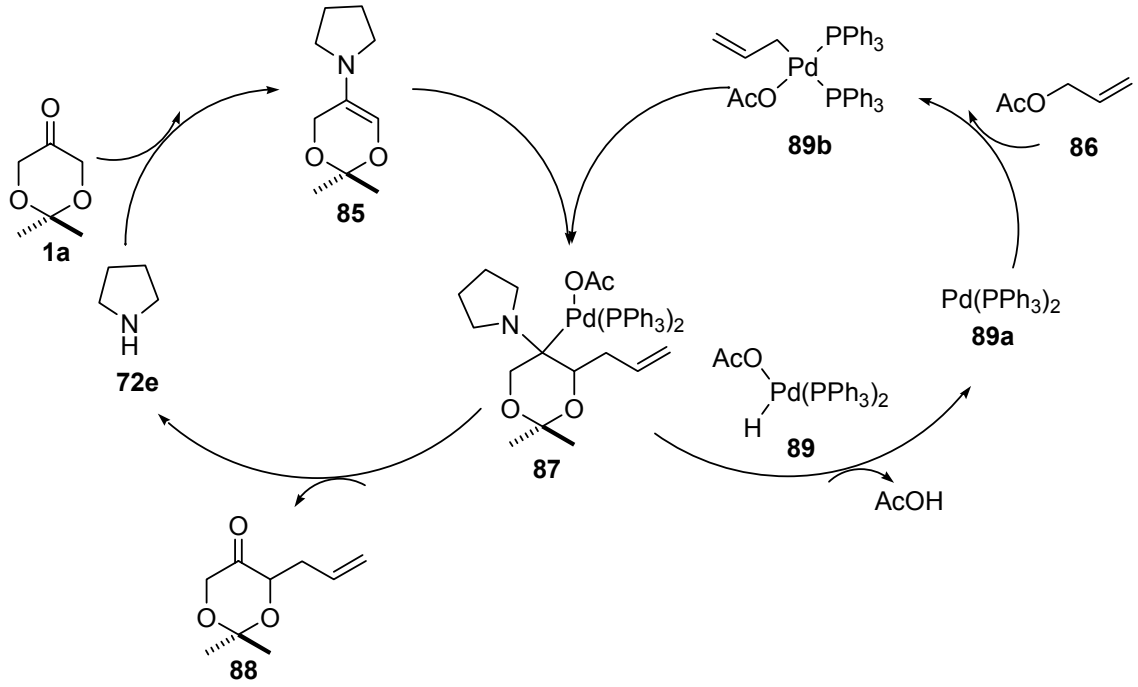



**Figure 1.11** The palladium/enamine catalytic cycle

## 1.5 Dioxanones in total syntheses

In the first section of the introduction I emphasized the importance of dioxanones and their effectiveness in synthesis of natural products or products that might possess an array of biological properties. Several natural products were synthesized based on Enders' SAMP/RAMP methodology. This section of my thesis will describe some selected examples of synthetic targets that were accomplished based on the dioxanone building block. I have deliberately excluded the hydrazone strategy, with only one exception, as the excellent review has been recently published which covers most of the achievements related to the total synthesis of compounds of interest based on the SAMP/RAMP approach.[9]

### 1.5.1 Synthesis of (+)-Frontalin

In 1998 our group[2] described the synthesis of (+)-frontalin – a pheromone playing an important role in chemical communication among insect species called mountain pine beetles. The retrosynthetic plan (depicted in Figure 1.12) involved alkylation of dioxanone **1** to form **93**. Next, sequential nucleophilic addition of methyl lithium to the carbonyl group, hydrolysis of acetals under acidic conditions, intermolecular acetalization and deoxygenation led to frontalin (**90**).

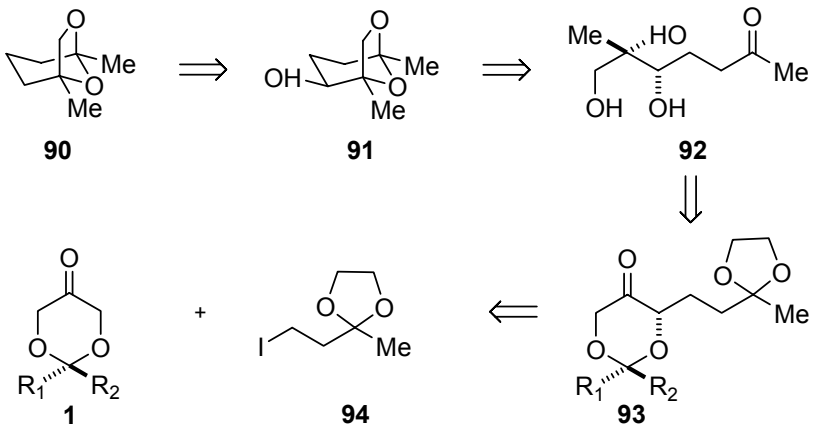
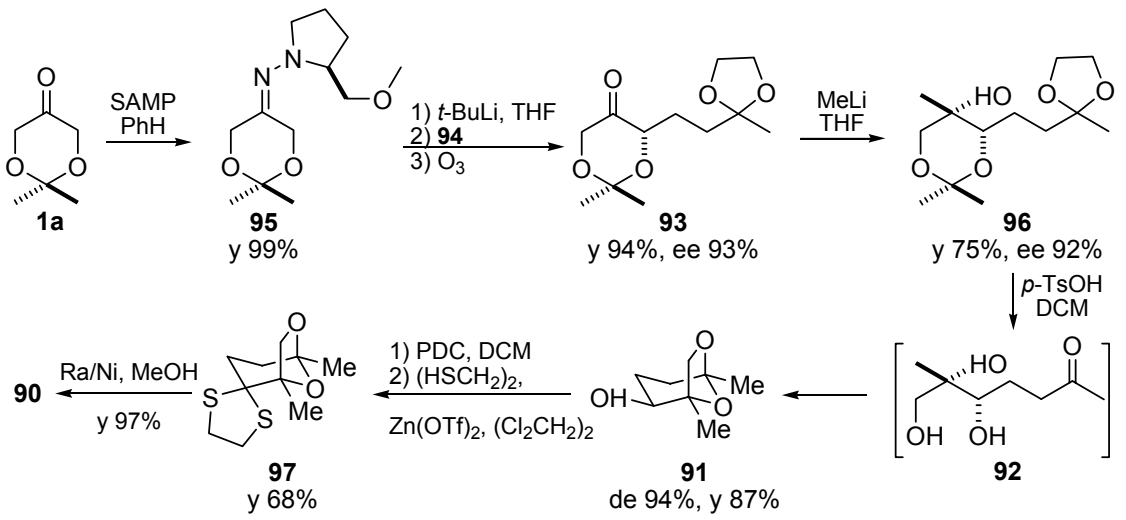



**Figure 1.12** Retrosynthetic plan for (+)-frontalin

The challenge in this synthesis was to find the method for enantioselective alkylation of **1**. Different protocols were investigated, including enantioselective deprotonation and method described by Francl,[71] however with no success. Then SAMP/RAMP methodology, well established and popularized by Enders,[73] was proposed for the first step (Scheme 1.30). Lithiation of **95**, followed by alkylation gave the desired product in 94 % yield and 96.5 to 3.5 enantiomeric ratio. Equatorial addition of MeLi to the carbonyl group, occurring from less substituted site, gave rise to alcohol **96** in 75 % yield and 96 : 4 diastereomeric ratio. Cleavage of the acetal functionality under acidic conditions provided intermediate **92**, which underwent spontaneous, highly selective (de 94), intermolecular acetalization in good chemical yield. Sequential, efficient oxidation, dithiane acetal formation and desulfurization afforded (+)-frontalin in 40 % overall yield in 7 steps starting from **1a**.

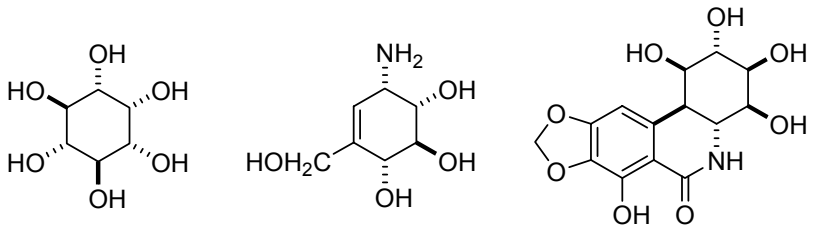



**Scheme 1.30**

### 1.5.2 Synthesis of (±)-7-deoxy-2-epipancratistatin tetraacetate

Polyhydroxylated cyclohexanes are known to be subunits in a number of biologically and pharmacologically relevant compounds. These include cyclitols[74] like *myo*-inositol (**98**) (Figure 1.13), which display a wide variety of crucial biological functions, or aminocyclitols[75] like valienamine (**99**), which is attracting attention due to

potential use as a chemotherapeutic agent. Recently, pancratistatin (**100**) gained interest as a synthetic target due to the potential antitumor properties.




**98** (*myo*-inositol) **99** (valienamine) **100** (pancratistatin)

**Figure 1.13** Structures of biologically active cyclitols

In 2006 Alonso[7] described a synthesis of a pancratistatin analogue **101**. The retro-analysis (Figure 1.14) showed that the target molecule could be prepared in sequence of chemical transformations starting from dioxanone **1a**.

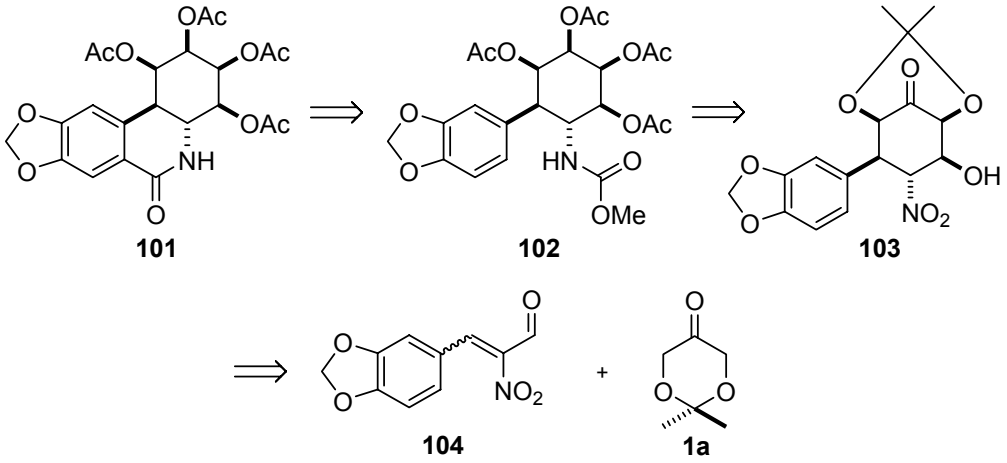
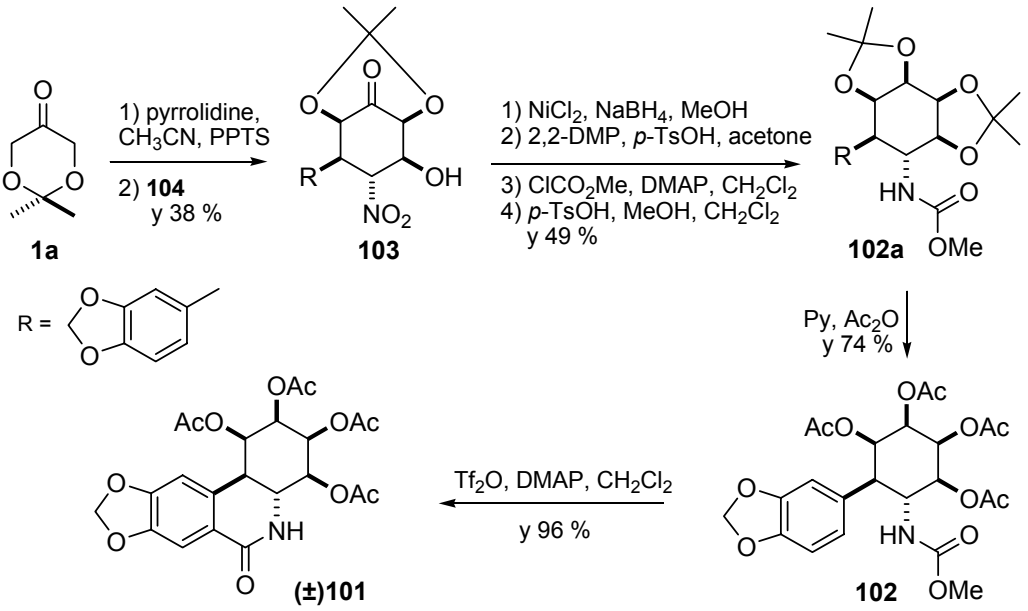



**Figure 1.14** Retrosynthetic plan for a pancratistatin analogue **101**

The challenge in this strategy was in annulation of β-aryl-α-nitro-α,β-enal **104** (prepared easily in a two steps from commercially available staring materials in 73 – 100 % yield as an inseparable mixture of E/Z isomers) with the enamine derived from 2,2-dimethyl-1,3-dioxan-5-one (**1a**). Initially, the attempts for this transformation,

allowing installation of five stereogenic centers in one step, proceeded with no success. However, after careful optimization of reaction conditions the product **103** was formed in 38 % yield as a single isomer. As outlined in Scheme 1.31 selective reduction of the carbonyl group was then required. It was achieved by using sodium borohydride in the presence of $NiCl_2$, and the hydroxyl groups were protected as acetonides. The nitro group, reduced simultaneously with the carbonyl in step 1 to the corresponding amino group, was converted into the methyl carbamate by using methyl chloroformate in the presence of DMAP forming **102a** in 49 % yield after four steps. Replacing the isopropylidene groups by acetyls using acetic anhydride in pyridine gave **102** in 74 % yield. Finally, cyclization afforded the desired product, (±)-7-deoxy-2-epipancratistatin tetraacetate (**101**) in seven steps and 10 % overall yield staring from dioxanone **1a**.

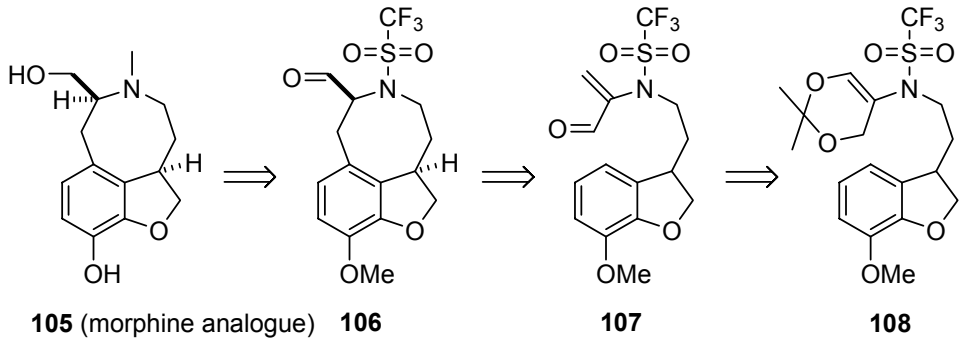



**Scheme 1.31**

### 1.5.3 Synthesis of a morphine analogue

The syntheses of a morphine analogue **105,** was reported by Funk[76] to show the usefulness of the methodology discovered in his laboratory. Retrosynthesis of **105,** depicted in Figure 1.15, demonstrated that the β-phenethylamine moiety could become available after reduction of the aldehyde, removal of triflamide and methylation of the

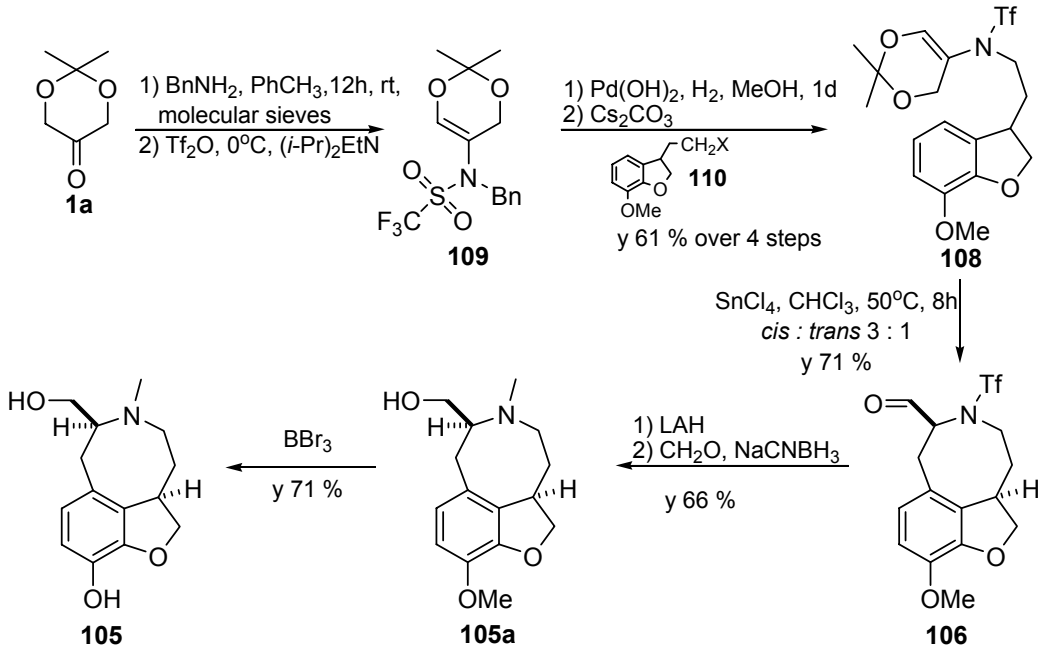
intermediate **106**. On the other hand, **106** could be obtained in Lewis acid catalyzed intramolecular electrophilic aromatic substitution from 5-triflamido-1,3-dioxin (**108**).




**105** (morphine analogue) **106** **107** **108**

**Figure 1.15** Retrosynthetic plan for formation of a morphine analogue **105**

This synthesis (Scheme 1.32) started with condensation of dioxanone **1a** with a primary amine and concomitant reaction with an anhydride in the presence of Hunig's base to form enamide **109**. Hydrogenation with Pearlman's catalyst followed by alkylation with the alkyl halide **110** provided the desired 5-triflamido-1,3-dioxin **108** in 61 % yield over four steps.




**Scheme 1.32**

Dioxin **108** underwent a facile Lewis acid catalyzed retrocycloaddition to form 2-amidoacrolein **107** which, upon cyclization *in situ* in the regioselective fashion, gave rise to benzazocine (**106**) in a 3 : 1 isomeric ratio and 71 % yield. Removal of the triflamide group and reduction of the aldehyde functionality to the corresponding alcohol were accomplished by treatment of the heterocyclic intermediate **106** with lithium aluminum hydride. The resulting secondary amine was methylated using sodium cyanoborohydride and formaldehyde in the standard reductive amination protocol. Boron tribromide was employed to cleave the methyl ether affording morphine analogue **105** in 20 % overall yield starting from dioxanone **1a**.

The syntheses of (±)-lennoxamine,[5] (±)-aphanorphine[5] and fasicularin[77] or (±)-euplotin[78] A are some of the examples proposed by Funk to demonstrate the usefulness of the 2-amidoacroleins derived from dioxins in synthesis of products of potential biological significance (Figure 1.16).

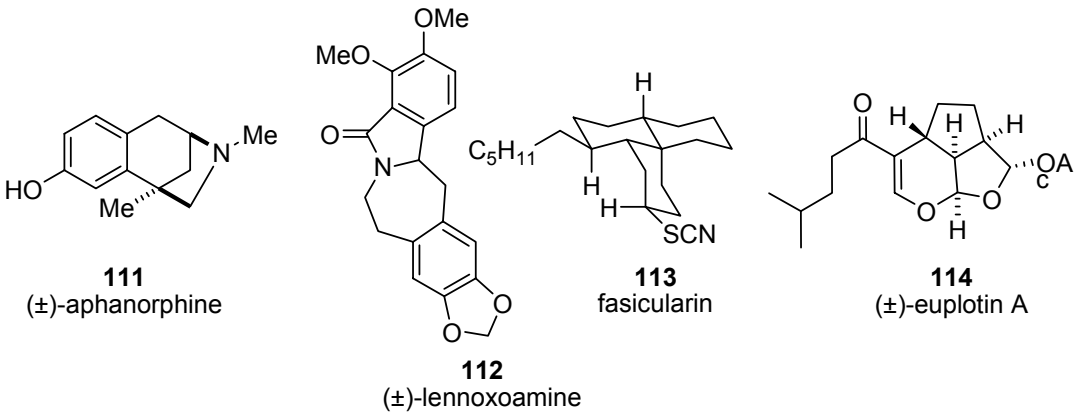
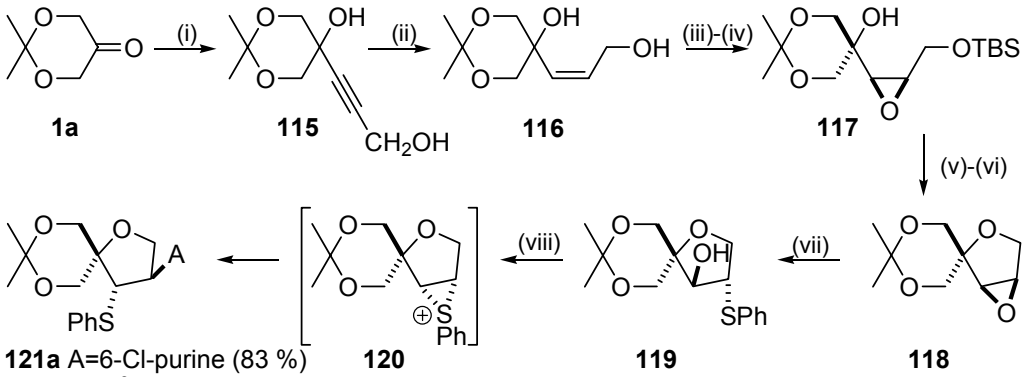



**Figure 1.16** Structures of biologically active compounds synthesized by Funk

### 1.5.4 Synthesis of (±)-Isonucleosides

Yoshimura described a novel methodology for synthesis of isonucleosides[79] (see Scheme 1.34, structures **123a** and **123b**), that have potential as a new class of anti-HIV nucleosides. The synthetic plan required a dioxanone as the building block to construct the isonucleoside skeleton.

In the first step ketone **1a** reacted with magnesium salt of propargyl alcohol in the presence of cerium chloride, providing diol **115** in 84 % yield, which was subjected to hydrogenation with a Lindlar catalyst. The corresponding (*Z*)-allyl alcohol **116,** upon selective protection with TBSCl, was treated with *m*-chloroperoxybenzoic acid (mcpba) to give the epoxide **117** in 90 % yield over two steps. Desilylation under standard conditions led to the formation of the corresponding epoxy alcohol which was subjected to intramolecular $S_N2$ cyclization using $PPh_3$ and DEAD in THF. The Mitsunobu reaction gave the desired dioxabicyclohexane derivative **118** in 94 % yield. Cleavage of the oxirane moiety was achieved in 95 % yield by treatment of **118** with thiophenol and sodium methoxide in methanol. The coupling of **119** with nucleobases was done under Mitsunobu conditions leading to the formation of purine isonucleoside derivative **121a** in 83 % yield and pyrimidine isonucleoside derivative **121b** in 52 % yield as single isomers (Scheme 1.33).

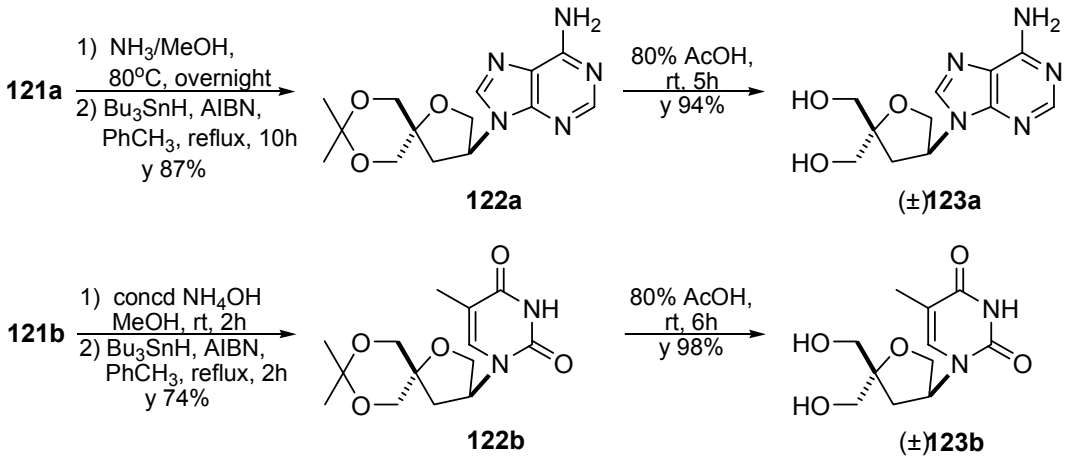



(i) $HC{\equiv}CCH_2OH$, *n*BuMgCl, $CeCl_3$, THF, 0°C, 1.5 h, 84% (ii) Lindlar cat., $H_2$, EtOH. rt, 7h, 91% (iii) TBSCl, imidazole, $CH_2Cl_2$, rt, 1h (iv) mcpba, THF, rt, overnight, 90% (v) TBAF, THF, rt, 1h, 99% (vi) $PPh_3$, DEAD, THF, rt, 1.5h, 94% (vii) PhSH, NaOMe, MeOH, reflux, 95% (viii) $N^3$-Bz-Thymine or 6-Cl-purine, $PPh_3$, DEAD, THF, rt, 3h

**Scheme 1.33**

Next the purine isonucleoside derivative **121a** was treated with methanolic ammonia followed by radical desulfurization with tributyltin hydride in the presence of AIBN. The resulting compound **122a** needed to be deprotected under acidic conditions to

provide desired 2',3'-dideoxy-4'-hydroxymethylisoadenosine (±**123a**) in 41 % yield in 11 steps starting from dioxanone **1a**. Similarly 3'-deoxy-4'-hydroxymethyliso - thymidine (±**123b**) was achieved in 23 % yield in 11 steps from **1a** (Scheme 1.34).



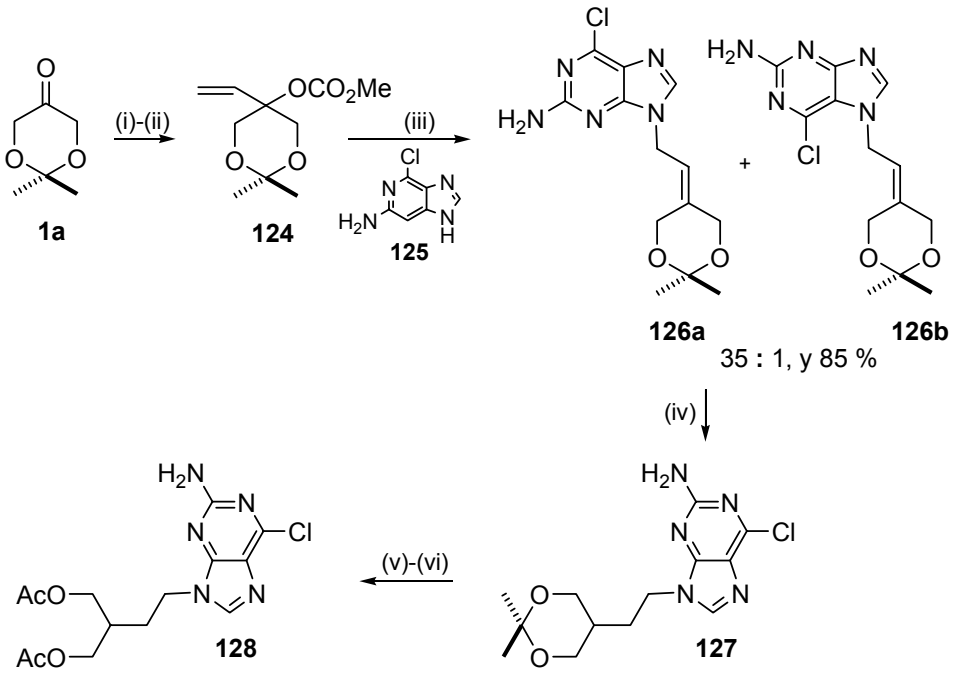

**Scheme 1.34**

### 1.5.5 Synthesis of Famciclovir

As indicated in the previous section, purine nucleosides are an important class of pharmacologically active compounds demonstrating activity against a wide range of viral infections.[80] In 2000 Smith described a synthesis of pharmaceutically important anti-herpes nucleoside analogue Famciclovir (**128**) *via* palladium (0) catalyzed coupling of 2-amino-6-chloropurine (**125**) and an allylic carbonate **124**. The dihydroxyacetone derivative, 2,2-dimethyl-1,3-dioxan-5-one (**1a**), provided a convenient starting point for the synthesis of the side chain of Famciclovir.

Reaction of **1a** with vinylmagnesium bromide and an in situ quench of the resulting alkoxide with methyl chloroformate afforded the allylic carbonate **124** in 73 % yield (Scheme 1.35). Next, coupling of **124** with the nucleoside base under different reaction condition was studied. A large number of catalyst/ligand combinations were investigated, however the best results were obtained when the mixture of $Pd_2dba_3$ and dppe were employed in a ratio of 1 : 2 in the presence of a catalytic amount (1 % mol) of $Cs_2CO_3$. To accomplish the synthesis, the facile reduction of the double bond and the

6-chloro group was carried on with hydrogen on palladium catalyst. Acid catalyzed hydrolysis of the acetonide followed by acetylation provided Famciclovir (**128**) in 53 % overall yield staring from **1a**.




(i) $CH_2$=CHMgBr, THF (ii) $ClCO_2Me$, 73% (iii) 5 mol% $Pd_2(dba)_2$,10 mol% dppe,1 mol%, $Cs_2CO_3$, DMF, 85% (iv) Pd(C), $H_2$, $Et_3N$, THF (v) MeOH, HCl, 93% (vi) $Ac_2O$, DMAP, $Et_3N$, DCM, 80%

**Scheme 1.35**

### 1.5.6 Synthesis of Azasugars

Iminocyclitols, also called "azasugars" are compounds in which the carbohydrate ring oxygen is replaced by nitrogen. Recently, these species attracted more interest as it was discovered that they might have the ability to act as potent inhibitors of enzymes involved in carbohydrate processing, such as glycosidases[81] and glycosyltransferases.[82, 83]

With an increasing interest in this class of compounds researchers started to look for viable synthetic routes to obtain those molecules. One of the efficient syntheses of

azasugars via the proline-catalyzed aldol condensation, outlined in Figure 1.17, was described by Fernandez-Mayoralas.[84]

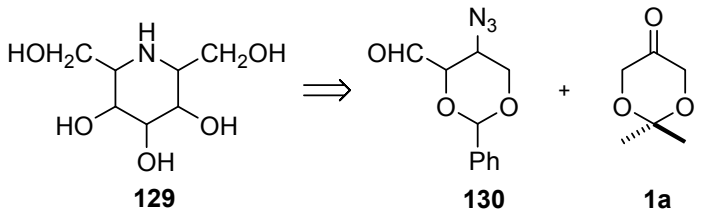
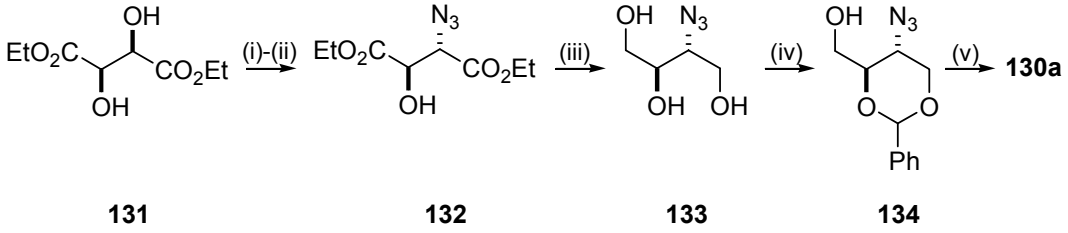



**Figure 1.17** Retrosynthetic plan of aminosugars by Fernandez-Mayoralas[84]

The approach presented in the retrosynthetic analysis required the appropriate aldehydes which were synthesized in enantiomerically pure forms staring from diethyl tartrate (**131**) in sequential route depicted in Scheme 1.36. This approach was viewed as especially attractive because tartrate derivatives were accessible in both enantiomerically pure forms. Moreover, racemic tartaric acid could serve as a good staring point for dynamic kinetic resolution on dioxanone system.

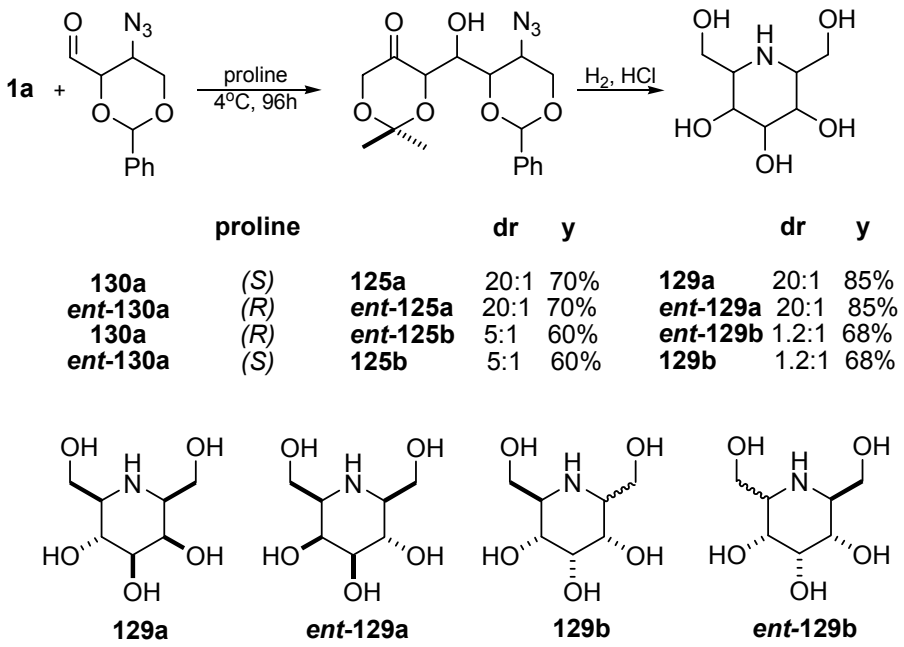



(i) $Et_3N$, thionyl chloride, 3h, 100% (ii) $NaN_3$, DMF, 5h, 70% (iii) $NaBH_4$, LiCl, EtOH, 4h, 63% (iv) benzaldehyde dimethylacetal, *p*-TsOH, MeCN, 3h, 45% (v) TEMPO, trichloroisocianuric acid, DCM, 0.5h, 60%

**Scheme 1.36**

Introduction of the azide group was achieved by nucleophilic attack on the cyclic sulfide formed from diethyl tartrate. Next step involved the reduction of diester **132** with $NaBH_4$/LiCl to the corresponding triol **133**, which underwent transketalation with benzaldehyde dimethylacetal and concomitant oxidation with TEMPO to afford desired aldehyde **130a**.

Next, the proline catalyzed reactions were carried on, followed by the reduction of the azide to the amine group. Finally, intramolecular reductive amination and acid-catalyzed deprotection of acetals provided four isomeric iminocyclitols (**129)** shown in Scheme 1.37.



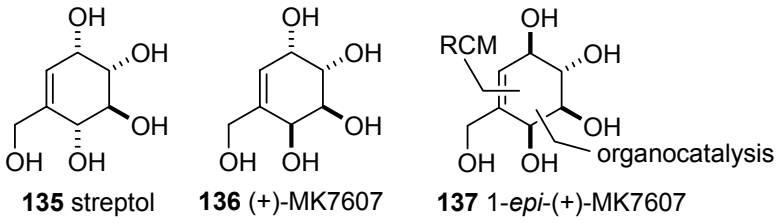

**Scheme 1.37**

Reaction of ketone **1a** with **130a** catalyzed by (*S*)-proline gave a mixture of *syn* and *anti* aldols in the ratio of 1 : 20 in 70 % yield. On the other hand, (*R*)-proline catalyzed aldol reaction preceded in a less selective fashion (dr 1 : 5), however in similar yield (60 %). The best results in terms of yield and stereoselectivity were obtained with matched substrate/catalyst pairs when **130a** was an acceptor and (*S*) enantiomer of proline was used as a catalyst, or in the combination of ***ent*-130a** and (*R*)-proline. This novel asymmetric route to obtain a diversity of iminocyclitols was successfully used in synthesis of glycosidase inhibitor *β*-homomannojirimycin (**129a**).

### 1.5.7 Synthesis of 1-*epi*-(+)-MK7607

(+)-MK7607 (**131**) and streptol (**135**) belong to the family of carbasugars. These "pseudo-sugars" differ from carbohydrates by the absence of the acetal functionality, in other words they are alicyclic analogs of monosaccharides, in which the usual ring-oxygen atom was replaced by the methylene group.[85] This feature is responsible for their stability towards hydrolysis. Carbasugars are interesting group of compounds because of their biological properties; for instance they act as glycosidase inhibitors, antibiotics, antivirals or plant growth inhibitors.[86]

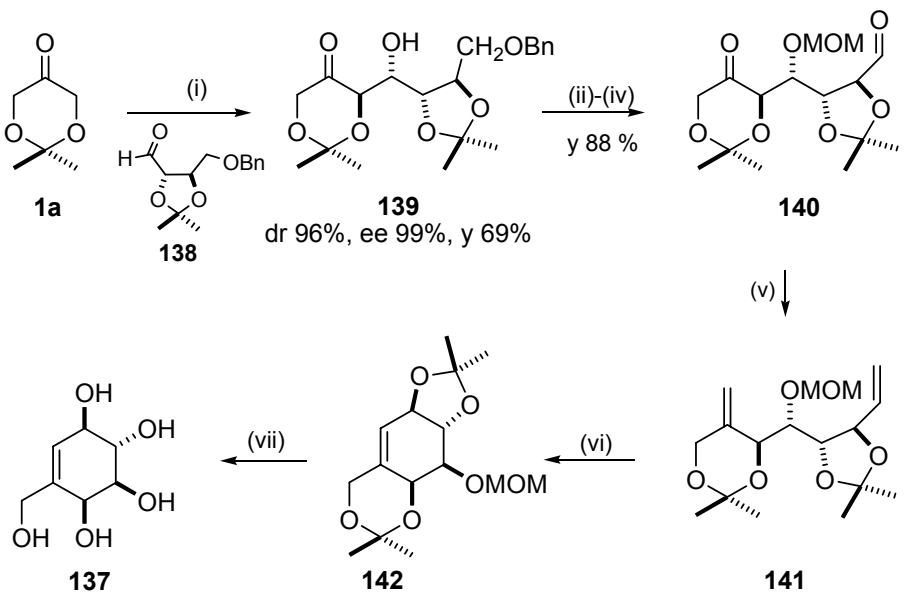
The synthesis of 1-*epi*-(+)-MK7607, proposed by Enders,[6] was achieved in the sequence of a proline-catalyzed aldol reaction and a ring-closing metathesis (see **137** in Figure 1.18).




**135** streptol **136** (+)-MK7607 **137** 1-*epi*-(+)-MK7607

**Figure 1.18** Selected examples of carbasugars

The synthesis of aldehyde **138** (Scheme 1.38)**,** compound which was required in organocatalysis, was prepared according to the Mukaiyama procedure[87] from the commercially available (*S*,*S*)-tartaric acid. Next, (*R*)-proline was employed to afford the product with fixed stereochemistry at the α and β positions. The desired product was formed in 96 % de, 99 % ee and moderate yield 69 %; however the aldolization proceeded in better yield then comparable reaction with the other enantiomer of the catalyst (37 %) (Scheme 1.38)




(i) (*R*)-proline, DMF, rt (ii) MOMCl, DIPEA, $Me_4NI$, DCM, rt, 99% (iii) Pd/C, $H_2$, 99% (iv) DMP, DCM, 0°C, 90% (v) $Ph_3PCH_3^+Br^-$, *t*-BuOK, THF, -78°C, 48% (vi) Grubbs' II, DCM, reflux, 90% (vii) DOWEX, MeOH, 70°C, 90%

**Scheme 1.38**

Aldol product **139**, after being successfully converted into the MOM ether using MOMCl in the presence of tertiary amine, was subjected to hydrogenolytic debenzylation and sequential Dess–Martin oxidation to form the corresponding dicarbonyl product **140** with an overall yield of 88 % over three steps.

Bisolefin **141**, obtained in 48 % using Wittig reaction with $Ph_3PCH_3Br$ and *t*-BuOK, was transformed into the cyclic moiety **142** via ring-closing metathesis employing Grubbs' second-generation catalyst in 90 % yield. Finally *epi*-(+)-MK7607 (**137**) was obtained upon acidic hydrolysis of tricyclic compound **142**.

## 1.6 Concluding remarks

In this chapter I have summarized the major issues which are related to the area of dioxanone chemistry which was the subject of my studies. In the literature review I focused mostly on the research that had been done by our group during the last 15 years.

Nonetheless, work of others was presented as well for comprehensivity of this chapter.

The problems with synthesis of dioxanones were outlined, followed by issues related to the enolization of dioxanones with lithium, boron and titanium reagents. Following that, enantioselective deprotonation with chiral lithium bases was briefly discussed and methods for absolute stereochemistry of deprotonation of dioxanones were described. Utility of the dioxanone chemistry was manifested in the synthesis of simple naturally occurring hexoses.

Following that, I have briefly described and discussed organocatalysis as a new method relevant to dioxanone chemistry. The power of this useful strategy found its application in the synthesis of protected sugars and their analogues.

A brief presentation of dioxanones as building blocks in selected examples of total syntheses of compounds of biological importance concluded this Introduction chapter.

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# CHAPTER 2

## 2. Results and discussion

This thesis deals with chemistry of 2,2-dialkyl-1,3-dioxan-5-ones (dioxanones) and with development of synthetic approaches to natural products using dioxanones as building blocks. In the previous chapter I have reviewed the key aspects of dioxanone chemistry that were elaborated by our group and by others. Below, the objectives of the research are briefly described, followed by presentation and discussion of the results.

The main aspect of the work was a methodology study aimed at expending the potential uses of dioxanones. Towards this end, the optimal conditions for the stereoselective aldol reaction, in which dioxanone would play a role of the nucleophile, were developed. Following this, the conversion of the dioxanone aldols to the corresponding α,α'- bis aldols had to be developed.

The synthetic focus of my project was on higher carbohydrates. Sugars are a group of compounds which possess a large number of functionalities: at least one carbonyl group and several hydroxyl functional groups per monosaccharide. Related compounds carry other kinds of functional groups like amino group (azasugars) or thiol group (thiosugars). Of the special recognition are carbasugars, in which the usual ring-oxygen atom is replaced by methylene.

In addition, sugars have several stereocenters and therefore can exist in a large number of stereoisomers. Carbohydrate chemistry, as a result of this structural complexity, has to deal with problems of regio- and stereoselectivity and of selective deprotection/protection of desired functional groups. It should be noted that isolation and purification of carbohydrates is often difficult.[1]

Higher carbohydrates are compounds composed of seven or more consecutive carbon atoms. They are known as subunits in a number of natural products of biological importance and are often used as chiral auxiliaries.[2, 3]

However, the synthesis of higher sugars has been a challenge in carbohydrate chemistry for more then a century. The synthesis starting from unprotected pentoses or hexoses is often difficult mainly due to low yields, poor diastereoselectivity and problems with isolation and purification. Some classical methods for a one carbon chain extension of aldoses involve the Kiliani (addition of cyanide) or the Sowden (addition of nitromethane) reactions.[4, 5] Other routes to higher sugars are based on the direct coupling of two appropriately chosen monosaccharide subunits containing many of the required stereogenic centers.[6]

## 2.1 Research objectives

**1)** To expand the chemistry of dioxanones with the aim of application in synthesis
   a) To investigate the reaction of dioxanones with different electrophiles,
**2)** To develop a new strategy towards the synthesis of higher sugars
   a) To investigate the reaction conditions for first aldol reaction
   b) To investigate the reaction conditions for the second aldol reaction
**3)** To develop methods for control of stereochemistry throughout the synthesis

The work presented in this thesis mostly describes progress towards synthesis of higher sugars based on the dioxanone building block according to the retrosynthetic plan shown in Figure 2.1

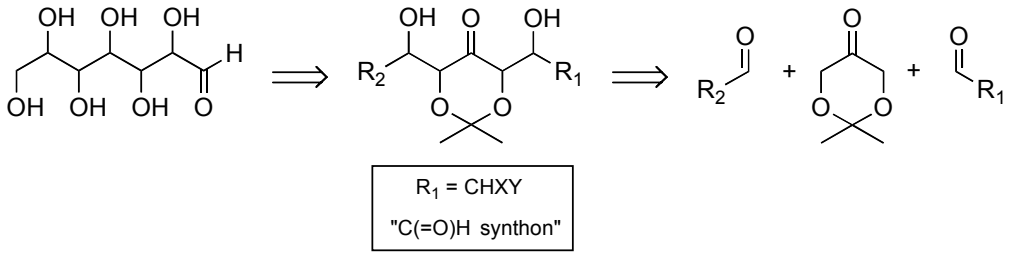
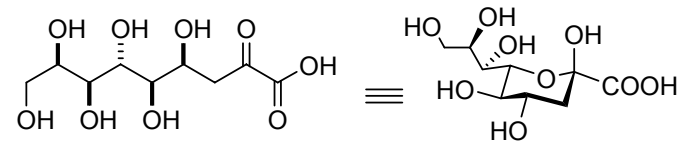



**Figure 2.1** Higher carbohydrates: retrosynthetic analysis

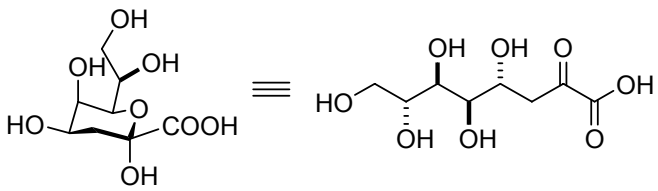
The key to this strategy was the connection of two carbon chains, containing a number of functional groups, at the α and α' positions of the dioxanone ring. This was envisaged via dioxanone enolate (or equivalent) chemistry. Depending on the specific target, different carbon-centered electrophiles varying in chain length and in functional groups would be required.

## 2.2 Functionalization of dioxanones at the α-position

As it is stated in my objectives I aimed on the methodology towards the synthesis of higher sugars. Early in my studies I became interested in developing of a strategy towards synthesis of ulosonic acids **KDN** and **KDO** (Figure 2.2). 2-Keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid (**KDN**), with its nine-carbon backbone, and 3-deoxy-D-manno-oct-2-ulosonic acid (**KDO**), with its eight-carbon skeleton, are classified as "higher carbon sugars" and have gained attention recently because of their biological significance. The eight carbon acidic sugar **KDO** is an integral component of the lipopolysaccharide (LPS) of Gram - negative bacteria. This unusual sugar is the first component of the oligosaccharide core region that links lipid A (a lipid component of an endotoxin held responsible for toxicity of Gram - negative bacteria) to the antigen.[7, 8] The sialic acid **KDN** was first isolated in 1986 from the polysialoglycoprotein of rainbow trout eggs.[9] Since then, quite a lot of its glycoconjugates have been reported to occur in various living organisms ranging from bacteria to mammals.[10] As a result several synthetic approaches were undertaken to obtain sialic acids and their analogues.[11] Typical synthetic routes to higher sugars involve homologation of lower carbon sugars and require introduction of new stereogenic centers in a controlled manner. I envisaged the bis - aldol strategy to accomplish the synthesis of these very interesting compounds. Some of the routes for synthesis **KDO**, **KDN** and their analogues have been already reported.[12, 13]




2-keto-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN)




3-deoxy-D-manno-oct-2-ulosonic acid (KDO)

**Figure 2.2** Structures of KDN and KDO

### 2.2.1 Retrosynthetic analysis of sialic acids

Retrosynthetically, an approach towards **KDN** could be envisaged *via* at least three different dioxanone-based strategies which are depicted in Figure 2.3. Route A described requires a connection of a one-carbon and a five-carbon fragment to the dioxanone building block. The success of route B would depend on the possibility of linking two and four carbon atom synthons to the dioxanone building block. Route C represents bonding of three different moieties, each of them composed of a three-carbon chain.

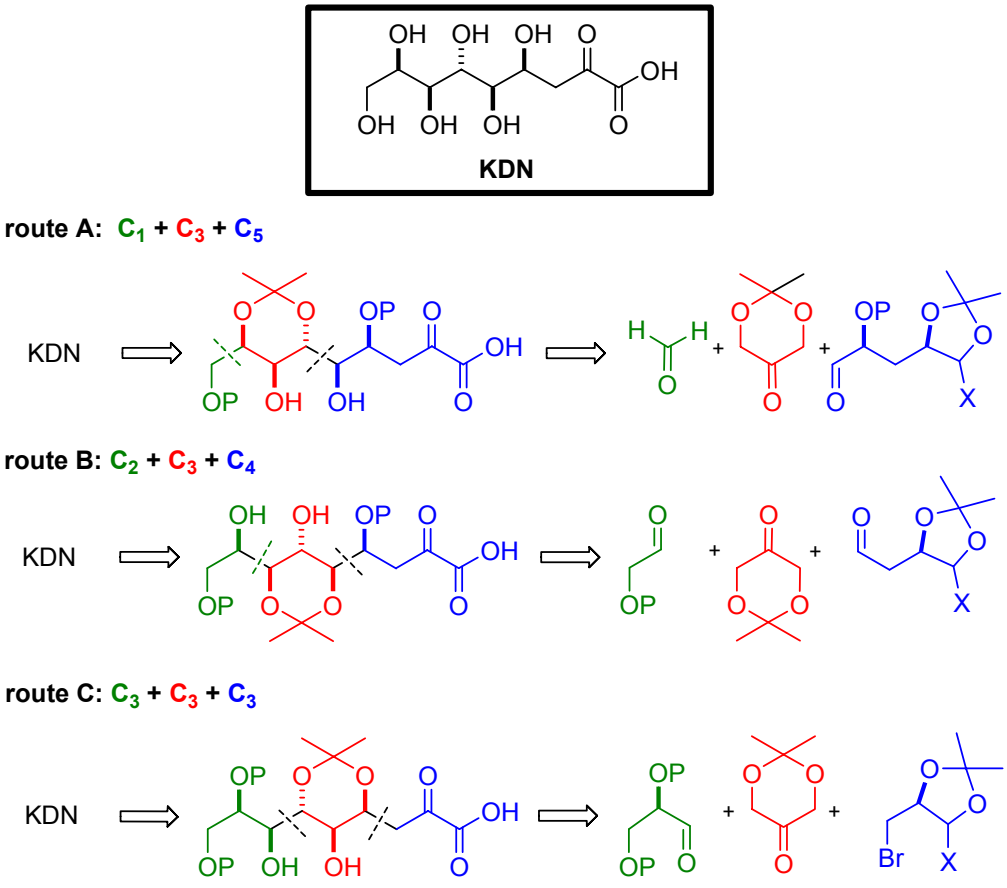



**Figure 2.3** Retrosynthetic analysis of KDN based on the dioxanone building block

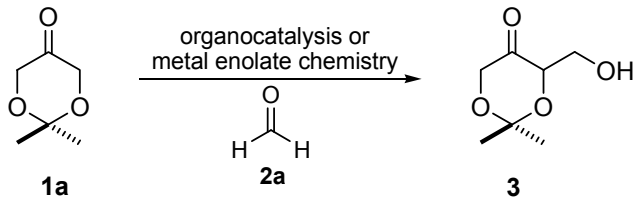
The choice of approach used for the generation of the sialic acid derivative seemed to be reasonably simple, but unfortunately the chemistry of the necessary aldol reactions

involving the required dihydroxyaldehydes was not well established. There were some precedents in the literature,[14-16] that referred to aldol and bis–aldol reactions, but those examples were related only to a limited number of aldehydes. Thus, one of the goals of the study aimed at the synthesis of sialic acid derivatives was to develop and optimize the conditions leading to the desired distribution of diastereoisomers and enantiomers in the aldol reaction and in the sequential double aldol reaction of dioxanones.

It should be noted that the difficulty level seemed even higher when we took into account the fact that some of the reagents were not commercially available. One could argue that the success of the synthesis of higher sugars based on the dioxanone building block would rest on the ability of introducing the appropriate one-, two- three-, four-, or five-carbon fragments and controlling stereoselectivity.

### 2.2.2 Introduction of one – carbon fragment onto the dioxanone system

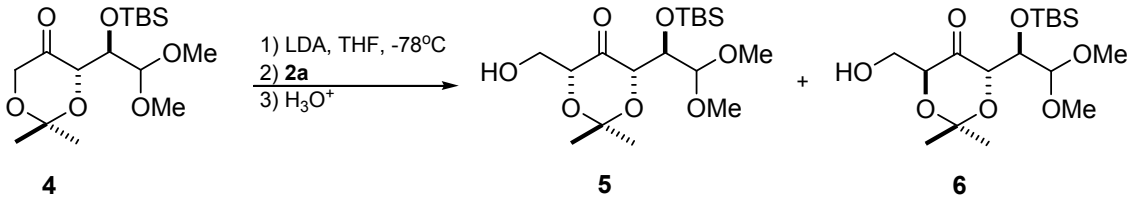
Following the retrosynthetic route A (Figure 2.3) in the forward direction would require the reaction of dioxanone enolate (or a synthetic equivalent) with formaldehyde. Thus, some approaches toward introduction of the formyl group at the α position were investigated.




**Scheme 2.1**

Nowak has previously reported a total lack of success when attempting to formylate dioxanone lithium enolate.[17] In my research, organocatalysis with proline emerged as an excellent method for dioxanone aldols (see section 2.3 below), however, in the (*S*)-proline-catalyzed aldol reaction of dioxanone **1a** with aqueous solution of formaldehyde (**2a**) the desired product was not formed. Changing the reaction

conditions (time, temperature and catalyst) led to the formation of a mixture that was difficult to separate and analyze. The lithium enolate chemistry provided the desired product in 12 % overall yield (Scheme 2.1). However, compound **3** was very unstable and quickly underwent further transformations and thus even the basic characterization ($^{13}$C NMR, MS, IR) was not possible. Formaldehyde is known to be very reactive and prone to polymerization. Moreover, aldol adducts have a general tendency to undergo dehydration and, sometimes, polymerization. Trapping of the formylated dioxanone with a silicon reagent *in situ* was undertaken, however this approach was unsuccessful. Perhaps the instability of **3** was associated with β-elimination of silanol and dimerization of α-methylene dioxanone in a manner similar to this of α-methylenecyclohexanone.[18] The lack of a good method for introducing a one-carbon fragment during the "first aldol" reaction was overcome by an advance in which the formylation was performed on the dioxanone aldol derivative **4** i.e. as the "second aldol" (Scheme 2.2).




**4** **5** **6**

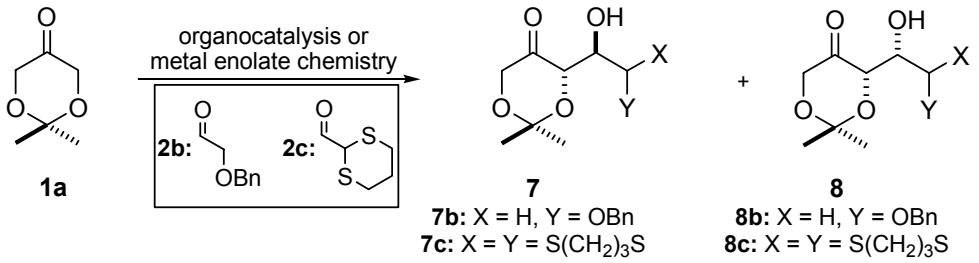
**Scheme 2.2**

The reaction of the lithium enolate of **4** and an excess of formaldehyde (gas) provided the mixture of **5** and **6** in a 2.3 : 1 ratio and in 29 % (39 % BORSM) overall yield. Those results were not satisfactory, although to the best of my knowledge this was the first example of direct formylation of dioxanone by means of lithium enolate chemistry.

### 2.2.3 Introduction of a two – carbon fragment onto the dioxanone system

Introduction of the two-carbon fragment was approached *via* either metal enolate chemistry or organocatalysis (Scheme 2.3). 2-Benzyloxyacetaldehyde (**2b**) and

1,3-dithiane-2-carbaldehyde (**2c**) were used as the acceptors. In the first case the desired aldol adduct was obtained in the boron-mediated process ($Chx_2BCl$, $Et_3N$, DCM, 0 °C). The reaction proceeded with excellent diastereoselectivity (1 : 99 *syn* : *anti*) and in high yield (82 %).




**Scheme 2.3**

Attempts to introduce the two–carbon fragment based on 2-benzyloxyacetaldehyde *via* either the lithium enolate (LDA, THF, -78 °C) method or organocatalysis ((*S*)-proline, DMSO, 4 °C) were not promising. In both cases formation of mixtures was observed. A simple experiment showed that **2b** not only had the tendency to freeze at -78 °C but also polymerized easily. The organocatalytic attempt involving this aldehyde went without success, even though this reaction had been previously reported.[19] α-Unbranched aldehydes usually did not furnish the desired products in high yields under standard conditions using DMSO as the solvent. Self-aldol addition of the starting material, condensation of the aldehyde or elimination of the cross-aldol product to α,β-unsaturated ketone appeared to be the main side reactions.

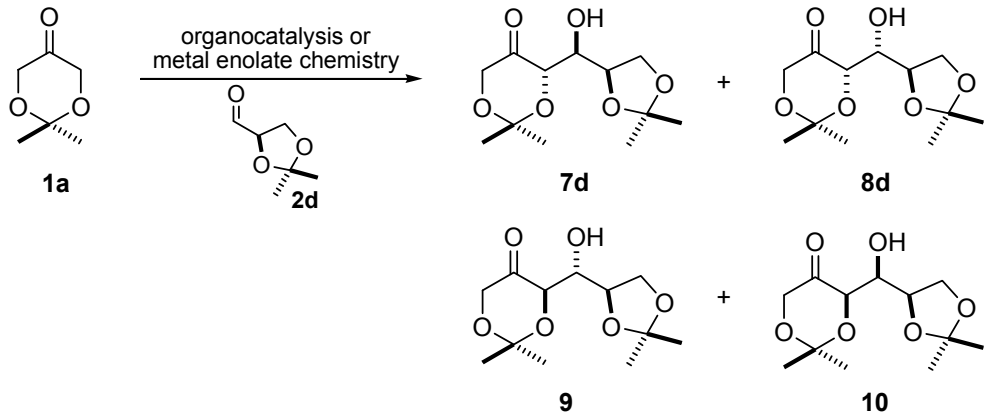
Reactions of dioxanone boron enolates in which 1,3-dithiane-2-carbaldehyde (**2c**), (a useful building block),[20] was used as the electrophile were then studied. Most reactions proceeded well, however the quench was found to be problematic. During the oxidative cleavage products that contained dithiane moieties underwent oxidation, leading to mixtures of undesired products. Investigation of different quench methods (Nowak methods: dimethyldioxirane, ethanolamine, sodium perborate and hydrogen peroxide)[21] did not give promising results, and thus this limitation caused the boron

enolate method to be ruled for inappropriate our synthetic objectives. I then turned to organocatalysis.

The proline-catalyzed aldol reaction of **1a** and **2c** proceeded well and the desired product was obtained in high diasteroselectivity and yield, although in low ee (66 %). However, the enantioselectivity problem was solved by optimizing the reaction conditions (see section 2.4 for more details).

### 2.2.4 Introduction of a three – carbon fragment onto the dioxanone system

There are several methods for three carbon atoms chain elongation of organic compounds with a number of interesting building blocks available.[22] As one of the examples, the aldol reaction with protected glyceraldehyde had been investigated in our group.[15] Lithium enolate chemistry of 2,2-dimetyl-substituted dioxanone and **2d** led to the formation of the aldol products in 70 % combined yield, although the diastereoselectivity was low (Scheme 2.4, Table 2.1, entry 3). Boron enolate derived from dicyclohexyl boron chloride and **1a** gave better distribution of isomers, however in moderate yield (Scheme 2.4, Table 2.1, entry 1).




**Scheme 2.4**

**Table 2.1** Aldol reaction of dioxanone **1a** with **2d** under different reaction conditions

| Entry | Method | Isolated yield [%] | dr<br>7d : 8d : (9 + 10) |
|---|---|---|---|
| 1 | A[a] | 59 | 85 : 15 : 0 |
| 2 | B[c] | 60 | 95 : 5 : 0 |
| 3 | C[c] | 70 | 53: 35:12 |

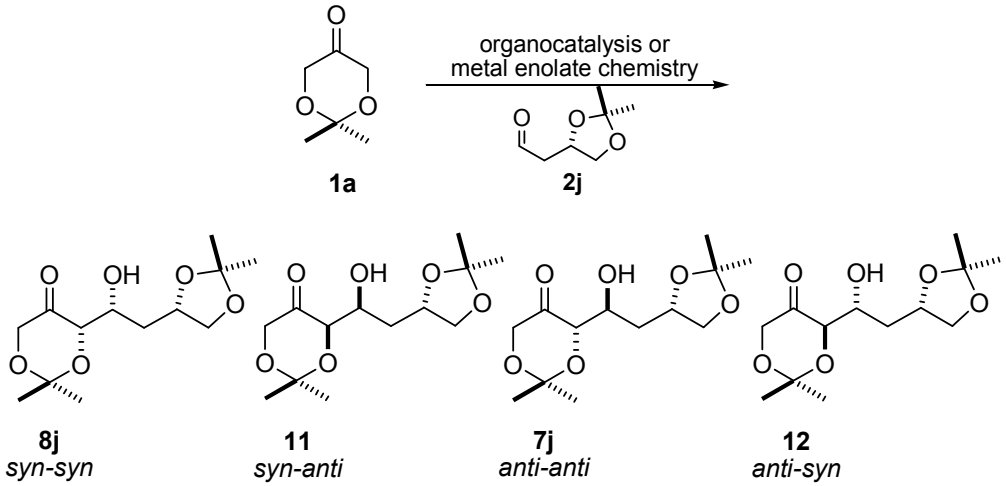
[a]$Chx_2BCl$, $Et_3N$,$CH_2Cl_2$, -78°C, DDO, [b](*S*)-proline, DMSO, 4°C, [c] LDA, THF, -78°C

It was decided to run this reaction using the organocatalytic route. The reaction proceeded well and although the final product was obtained in a moderate yield (60 %) the high diastereoselectivity level was reached (Scheme 2.4, Table 2.1, entry 2).

### 2.2.5 Introduction of a four – carbon fragment onto the dioxanone system

A possibility of connecting a four-carbon fragment to the dioxanone ring was briefly investigated by means of the aldehyde **2j** which was synthesized in 65 % yield in 4 steps from the commercially available (*S*)-malic acid.[23]

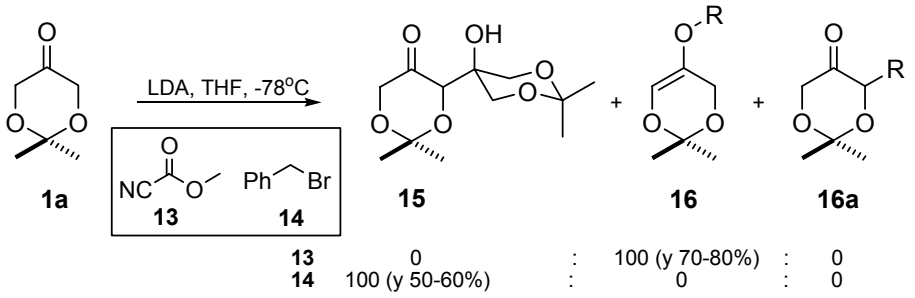
Unfortunately, this interesting compound and potential building block for synthesis of 7-carbon sugars, practically in one step caused a number of problems. An organocatalytic attempt ((*S*)-proline, DMSO, 4 °C) did not work well, since most probably the self aldolization of the aldehyde occurred. The crude reaction mixture, besides a large amount of the unreacted starting ketone contained the desired product in an approximately 6 - 10 % yield as a mixture of *syn* and *anti* isomers in a nearly 1 : 1 ratio. In addition, the products were found to be very difficult to fractionalize by column chromatography and only partial separation was achieved. Based on the results from this experimentation (together with observations described above c.f. 2.3.3) led me to believe that β-branched aldehydes might have a tendency to undergo self addition under proline catalysis conditions. Rather than desired pathway in which proline reacts with the ketone to form the reactive intermediate that upon addition of the aldehyde and hydrolysis would give rise to the aldol product, the catalyst facilitated the self condensation of the aldehyde.




**Scheme 2.5**

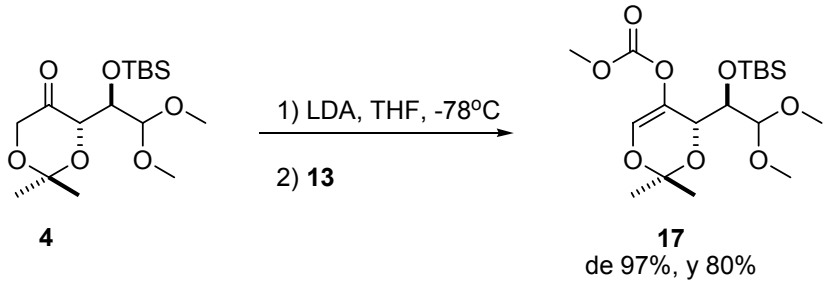
Boron enolate chemistry ($Chx_2BCl$, $Et_3N$, DCM, 0 °C) was tried as the tool for introducing this useful four-carbon fragment. The reaction proceeded with a moderate yield (71 %) and low diastereoselectivity (72 : 18 : 10). Only one of the isomers was isolated in low yield and tentatively assigned to be the *anti-anti* product **7j** (Scheme 2.5).

In the foregoing sections the use of the aldol reaction to connect a new fragment (hydroxyalkyl chain) to the dioxanone ring was described. The introduction of the alkyl or acetyl moiety to the dioxanone system was proved to be not easy. Efforts to connect an alkyl chain or an ester functional group at the α-position via the lithium enolate or organocatalysis were not successful. Both methods did not look promising and, in most cases, only the dioxanone dimer (**15**) was formed in 50 - 60 % yield. On the other hand reaction of lithium enolate of **1a** with methyl cyanoformate provided the O-acylated products **16** were isolated in 70 - 80 % yield (Scheme 2.6).




**Scheme 2.6**

Similarly, an attempt to functionalize the α'-position of a dioxanone aldol derivative by the means of the alkylation or acylation did not give the desired products. Reaction with alkylating reagents gave unchanged staring material after the aqueous work-up; on the other hand Mander's reagent gave rise to the corresponding O-acylated product **17** in up to 80 % yield (Scheme 2.7).

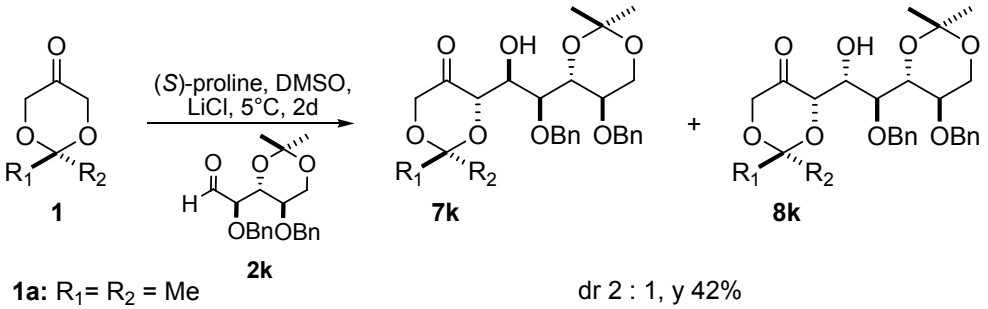



**Scheme 2.7**

### 2.2.6 Introduction of a five – carbon fragment onto the dioxanone system

Connection of a five carbon fragment to the dioxanone building block *via* organocatalytic aldol reaction was developed in our group by Palyam[24] (I only present this here for the sake of completeness). The required aldehyde, protected ribose (**2k**), was prepared from dioxanone in a 4 step synthesis (sequence of organocatalytic aldol reaction, reduction of the carbonyl group, benzylation and dithiane hydrolysis) in 56 % overall yield. (*S*)-Proline catalyzed direct aldol reaction of **1a** and **2k** in the presence of

LiCl gave two isomeric products in 42 % yield and low selectivity. Those results could be improved by changing the substitution on dioxanone ring from methyl to *tert*-butyl. Then the desired product was formed in 56 % yield and 9 : 1 *anti* to *syn* ratio (Scheme 2.8).




**1a:** $R_1 = R_2$ = Me dr 2 : 1, y 42%

**1b:** $R_1$ = *t*-Bu, $R_2$ = Me dr 9 : 1, y 56%

**Scheme 2.8**

### 2.2.7 Conclusions

Methods for connecting polyoxygenated one-, two- three-, four- and five-carbon fragments to the dioxanone system were investigated. Formylation was feasible only on the dioxanone derivative (as the "second aldol"), however both the diastereoselectivity and the yields were low (dr 2.3 : 1, yield 29 %, 39 % BORSM). Simple dioxanone **1a** was formylated leading to the unstable product in 12 % overall yield. The two- and three- carbon fragments could be relatively easily introduced at the α-position of the dioxanone ring by using either enolate chemistry or organocatalysis.

Unfortunately, no good method for connecting a four- carbon chain suitable for further carbohydrate synthesis was found. The (*S*)-proline catalyzed reaction gave mostly aldehyde adducts, which are easily formed under reaction conditions. Enolization with $Chx_2BCl$ in the presence of triethylamine proceeded in 72 % yield albeit formation of isomeric, inseparable products discredited this useful staring material from further use.

Alkylation and acylation attempts were not successful (in agreement with previous reports)[21] and led to the formation of dimeric adduct of dioxanone or to O-acylated products.

A five-carbon moiety was attached to the dioxanone ring by using organocatalyzed direct aldol reaction. This protocol was employed in synthesis of protected D-glycero-D-manno-2-octulose.[24]

This investigation showed that different in length carbon fragments might be successfully installed in the dioxanone building block. Selectivities and yields depended on the method and nature of the electrophile; however one to five carbon chains were possible to connect to simple dioxanones or its derivatives. Alkylation did not look promising as a dimer of dioxanone was the major component of the reaction mixture. On the other hand acylation reaction with the methyl cyanoformate provided exclusively O-acylated product.

**2.3 Organocatalytic aldol reaction of dioxanones: a methodology study**

Aldol reactions of dioxanones had been extensively studied in our laboratories for more then 15 years. During this time it was established that deprotonation (including enantioselective deprotonation) of this very useful building block could be achieved *via* lithium and boron enolate chemistry.[25-27] Some of the problems, such as addition of LDA to the carbonyl group or low selectivity, were defeated by careful optimization of the reaction conditions,[25] choice of the dioxanone substrate and choice of the chiral amine and by addition of lithium salts[28] (see Chapter 1.2 in the Introduction part for details). As the result some simple protected carbohydrates, such as D-tagatose and D-psicose, were synthesized in a one step procedure in good selectivities and yields (see chapter 1.3 in the Introduction part for details). To the best to my knowledge those examples were the first syntheses of protected sugars based on the dioxanone building block. During this work, the absolute stereochemistry of dioxanone aldols had also been determined by correlation with natural products.[27]

In my studies I had chosen organocatalysis as a promising and simple method for generating the needed optically pure compounds. When this project was started,

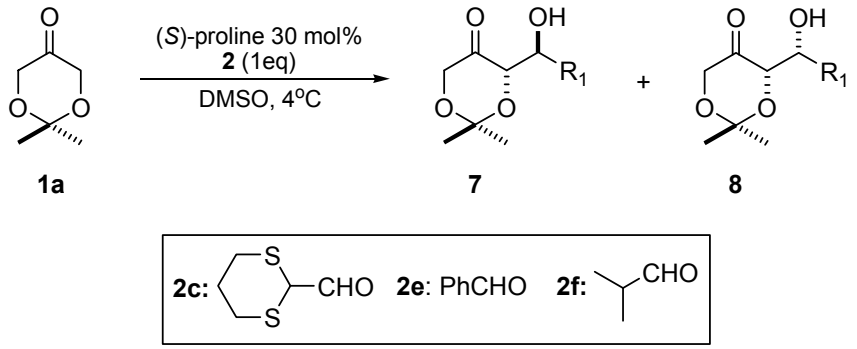
there was no information in the literature concerning organocatalytic reactions involving dioxanones. During the investigation that followed, I faced a lot of problems with reproducibility, selectivity and yields. Observations resulting from these studies led to better understanding and improvements of the method which are described in detail in the following section. The underlying theme in these studies was the application to synthesis of carbohydrates that was envisaged through a sequential aldol - aldol approach (c.f. the retrosynthetic analysis in Figure 2.1).

### 2.3.1 The "first aldol": role of additives in the aldol reaction catalyzed by (*S*)-proline

As indicated above, there were a few problems associated with synthesis of polyoxygenated compound *via* a double aldol strategy starting from the dioxanone building block. Selectivity in the first aldol reaction could be achieved by employing enantioselective deprotonation. However, looking for a simpler and cheaper method I became interested in organocatalysis as a key transformation for making β-hydroxy derivatives of dioxanone with (*S*)-proline as the catalyst. The attractiveness of this approach is rising very fast and it is expressed in the very large number of publications on the topic within recent years. I explored organocatalysis of dioxanone aldol using proline, when this project was under way other researchers reported that this method worked well with dioxanones.[19, 29-31] The choice of the catalyst was dictated by the fact that (*S*)-proline is an inexpensive, commercially available compound. Moreover, proline is accessible in both enantiomeric forms and it can be easily removed from the reaction mixture by aqueous workup.

At the beginning, attempts to effect proline catalyzed aldol reaction involving the simple dioxanone met with limited success. Reactions done in dry solvents (DMF or DMSO) proceeded with poor reproducibility, moderate selectivities, often with mediocre enantioselectivity and poor yields. This might have been caused by impurities which were difficult to remove completely, such as dimethylamine in DMF. Dimethylamine could compete with (*S*)-proline in the imine formation step leading to

lowering of ee values. Preliminary results indicated superiority of DMSO over DMF, therefore the former solvent was used in the series of (*S*)-proline catalyzed aldol reactions. Results are summarized in Scheme 2.9 and Table 2.2.




**Scheme 2.9**

**Table 2.2** Proline catalyzed aldol reaction of dioxanone **1a**

| Entry | $R_1CHO$ | Time (days) | Isolated yield [%] | dr (*syn*:*anti*) | ee (*anti*)[%] |
|---|---|---|---|---|---|
| 1 | **2c** | 3 | 78 | > 99 | 66 |
| 2 | **2e** | 7 | 54 | 36: 64 | 68 |
| 3 | **2f** | 3 | 65 | > 99 | 86 |

Reactions proceeded with modest enantioselectivieties (from 66 % to 86 %) depending on the aldehyde. Since such selectivities were not satisfactory from the target oriented synthesis, I focused on running the reactions with an intentional addition of Bronsted or Lewis acids, as some uses of these compounds had already been described.[32-34] The selection of the additive had to be limited to weak acids only, so they would not react with the substrate, since dioxanones are known to be sensitive to acids. Use of relatively strong acids, such as camphorsulphonic acid monohydrate (CSA) or *para*-toluenesulphonic acid monohydrate (*p*-TsOH·$H_2O$) was tried as well, but as

predicted they led to decomposition of the starting dioxanone. The summary of results at these studies is presented in Table 2.3.

**Table 2.3** Proline catalyzed aldol reaction of dioxanone **1a** in the presence of additives

| Entry | $R_1CHO$ | Additive (eq) | Time (days) | Isolated yield [%] | dr[a] (*syn*:*anti*) | ee[b] (*anti*)[%] |
|---|---|---|---|---|---|---|
| 1 | **2c** | - | 3 | 78 | > 99 | 66 |
| 2 | **2c** | $H_2O$ (0.1) | 3 | 84 | > 99 | 66 |
| 3 | **2c** | $H_2O$ (3) | 2 | 80 | > 99 | 90 |
| 4 | **2c** | PPTS (1) | 3 | 83 | > 99 | 93 |
| 5 | **2c** | LiCl (1.5) | 3 | 85 | > 99 | 90 |
| 6 | **2e** | - | 4 | 54 | 36 : 64 | 68 |
| 7 | **2e** | LiCl (1.5) | 4 | 85 | 29 : 71 | 86 |
| 8 | **2e** | PPTS (1) | 4 | 61 | 18 : 82 | 86 |
| 9 | **2f** | - | 3 | 80 | > 99 | 86 |
| 10 | **2f** | LiCl (1) | 3 | 74 | > 99 | 92 |
| 11 | **2f** | PPTS (1) | 3 | 70 | > 99 | 96 |

[a] dr was measured by $^1$H NMR on the crude reaction mixture, [b] ee was measured by $^1$H NMR on pure (*anti*) isomer with $Eu(tfc)_3$ or (*S*)-(+)-TFAE as shift reagents

The enantioselectivity of the aldol reaction in the dioxanone system was clearly improved by addition of pyridinium *para*-toluenesulphonate (PPTS) or lithium chloride. Of the three aldehydes which were tested, aldehyde **2c,** showed average selectivity in dry DMSO (table 2.4, entry 1), but the selectivity visibly improved in the presence of 3 molar equivalents of water as well as in the presence of PPTS or LiCl (entries 3, 4, 5). Aldehydes **2e** and **2f** behaved similarly, but the differences between additive-free conditions and running the reactions in the presence of acids were much smaller in the

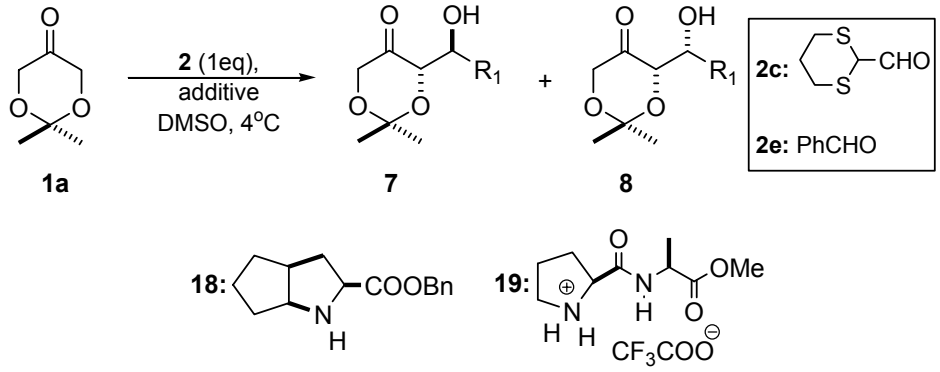
case of compound **2f**, in agreement with the previously described trend of aliphatic α - branched aldehydes to be most stereoselective in this type of reactions.[35]

### 2.3.2 Other catalysts in direct dioxanone aldol reaction

Next, my attention was turned toward screening other amino acids that might be potential catalysts in organocatalytic aldol reactions. There was limited information in the literature on that aspect of organocatalysis and proline was widely believed to be the best catalyst.[36.] Simple amino acids are known to play important roles in biological systems, so my expectation towards simpler molecules than proline to be good catalysts in the aldol reaction (which is also one of the most important reactions in Nature) was reasonable. Results are presented in Scheme 2.10 and Table 2.4.

Use of non-cyclic amino acids: alanine, phenylalanine, lysine and valine led to low yields (alanine, in the absence of additives, did not show any catalytic activity) and, in general, lower selectivities. Use of PPTS as the additive resulted in better yields and higher selectivities, but the increases were small. Where the investigations were in the progress a report by Cordova had appeared, describing a very notable effect of water in reactions catalyzed by linear amino acids.[37]

Catalytic properties of compound **18** were briefly examined. It has been reported by others that this compound, an analogue of a proline ester, did not catalyze the aldol reactions of dioxanones (the experiments were done without any additives).[38] In my hands, in the presence of PPTS, the reaction proceeded with good enantioselectivity, albeit in low yield (Table 2.4; entry 1). That seemed to signal the need to re-evaluate the nature of the transition state involved in the proline catalysis. The simple dipeptide **19** was synthesized (by coupling of *t*-Boc protected (*S*)-proline and (*S*)-alanine methyl ester) and tested as the catalyst. Protection of the carboxyl group was intentional, so we could investigate the reaction conditions and support our hypothesis that carboxylic group does not have to take part in the catalytic system as it was believed and mostly presented in the literature.[39-41] The reaction proceeded in good yield; however the desired products were formed in low diastereoisomer ratio (Table 2.4, entry 2).




**Scheme 2.10**

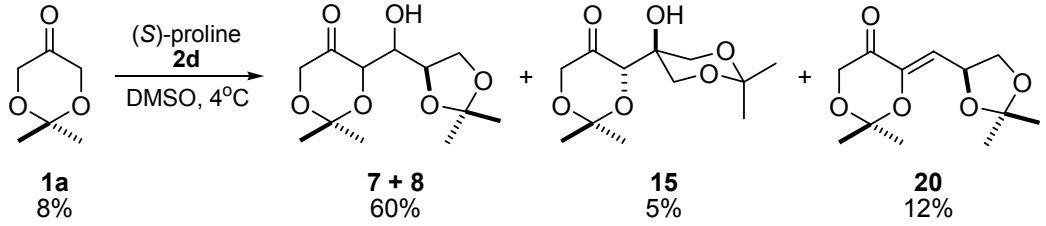
**Table 2.4** Effects of other catalysts on aldol reaction

| Entry | $R_1CHO$ | Catalyst[a]/ Additive | Time (d) (temp) | Isolated yield [%] | dr[b] *syn*:*anti* | ee[c] (*anti*)[%] |
|---|---|---|---|---|---|---|
| 1 | **2e** | **18** / PPTS | 4 (6 °C) | 20 | 1 : 5.2 | 82 |
| 2 | **2e** | **19** / PPTS | 4 (6 °C) | 78 | 1 : 2.6 | 90 |
| 4 | **2c** | (*S*)-Ala | 5 (r.t.) | 3 | - | - |
| 5 | **2c** | (*S*)-Ala/PPTS | 5 (6 °C) | 20 | 1 : 24 | 84 |
| 6 | **2c** | (*S*)-Phe | 5 (r.t.) | 35 | 1 : 9 | 68 |
| 7 | **2c** | (*S*)-Phe/PPTS | 5 (6 °C) | 39 | 1 : 13.3 | 78 |
| 8 | **2c** | (*S*)-Lys HCl | 5 (r.t.) | 33 | 1 : 15.7 | 90 |
| 9 | **2c** | (*S*)-Lys HCl | 5 (6 °C) | 36 | 1 : 32.3 | 82 |
| 10 | **2c** | (*S*)-Lys/PPTS | 5 (6 °C) | 28 | 1 : 24 | 88 |
| 11 | **2c** | (*S*)-Val/PPTS | 5 (6 °C) | 29 | 1 : 15.7 | 64 |
| 12 | **2c** | (*S*)-Pro | 5 (r.t.) | 88 | 1 : 8.1 | 66 |

[a] 30 mol% of the catalyst was used, [b] determined by $^1$H NMR on crude reaction mixture, [c] determined on pure sample by $^1$H NMR technique using $Eu(tfc)_3$ or (*S*)-(+)-TFAE

### 2.3.3 Limitations of the organocatalytic direct aldol reaction of dioxanones

Despite its utility, versatility and simplicity (*S*)-proline-catalyzed aldol reaction of dioxanone has a few limitations. Even though those reactions usually proceed in high selectivieties and moderate to high yields, usually the crude reaction mixtures contain unreacted starting materials, dioxanone dimer and dehydrated aldol products. The amounts of the dimer (up to 30 %) and undesired dehydrated products (up to 20 %) typically depend on the substrate; however no general trend could be observed. In the reaction of 2,2-dimethyl substituted dioxanone with (*R*)-glyceraldehyde (**2d**) catalyzed by proline the starting material **1a** was recovered in 8 %, self-aldol addition product **15** was isolated in 5 % yield, and the product of elimination of the cross-aldol **20** was isolated in 12 % yield (Scheme 2.11).




**Scheme 2.11**

Moreover, as had already been reported by List,[41] some ketones like acetophenone, 3-pentanone, tetralone and other important staring materials failed to react under our reaction conditions (Figure 2.4).

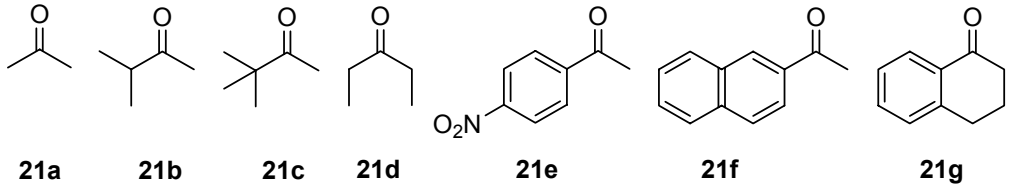



**Figure 2.4** Ketones that failed to react in (*S*)-proline catalyzed aldol reaction under conditions developed in our laboratories

### 2.3.4 Attempts to rationalize the influence of additives

The organocatalytic methodology was successfully applied to dioxanone aldol reactions allowing synthesis of a number of products with moderate selectivities and in good overall yields. The enantioselectivity was often enhanced by addition of weak Lewis or Bronsted acids as co-catalysts.[42] Especially worth mentioning are pyridinium *para*-toluenesulphonate (PPTS, a weak Bronsted acid) and lithium chloride (a weak Lewis acid) which exerted a major effect on the stereoselectivity of the proline-catalyzed aldol reactions of dioxanones. While reactions run without additives might not be synthetically useful, these additives moved the selectivity into the synthetically attractive range (from 66 up to 92 % ee depending on the substrate). Moreover the acidic additives proved that the carboxylic group might not play as important a role in catalytic cycle as it was believed.

Investigations together with mechanistic and kinetic studies by Hajos,[43] Houk[44] and Agami[45] led to the proposal of models that are commonly accepted and used to support the discussion of aldol reaction with (*S*)-proline. In the Houk model (Figure 2.5) the enamine reacts with the carbonyl compound (aldol acceptor) under activation *via* hydrogen – bonding to proline's carboxylic acid group. This model was supported by $^{1}$H NMR experimentation and is considered the most popular. In contrast, in the Agami model the enamine reaction with the aldol acceptor is mediated by the second proline molecule (Figure 2.5).[33, 46, 47] In my case one could suggest a dual: enamine – Lewis acid model in which lithium is complexed both to the nitrogen and the C=O of proline, as well as to the carbonyl group of the acceptor.

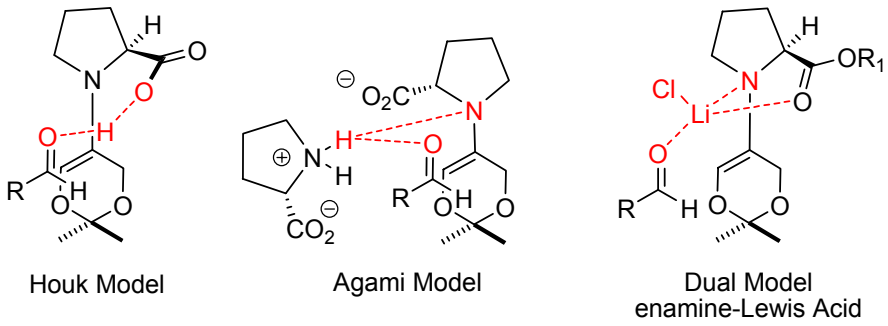



**Figure 2.5** Models in proline catalyzed aldol reactions

The role of the Lewis acid in a direct aldol reaction with catalytic amounts of (*S*)-proline is not clear. Some of the explanations for the observed changes in selectivity could be as follows: when a metal compound is added to the reaction mixture containing water (note that water is released during the imminium formation – see the catalytic cycle in Figure 1.8 or 2.7), the metal salt dissociates and hydration takes place immediately. If an aldehyde is present in the system, there is a chance for it to coordinate to the metal cation ($Li^+$ in our case) instead of the water molecule (the intra- and intermolecular reactions of water molecules might occur as water is present all at times in the catalytic cycle), and the aldehyde is then activated. An enamine attacks this activated aldehyde to produce the aldol adduct. According to this mechanism, it might be expected that Lewis acid catalyzed reactions should be successful in solutions that contain at least traces of water.[48]

Another mechanism for the proline catalyzed aldol reaction with participation of metal salts might be based on kinetic studies which have been published recently by Reymond et al. (Figure 2.6).[49]

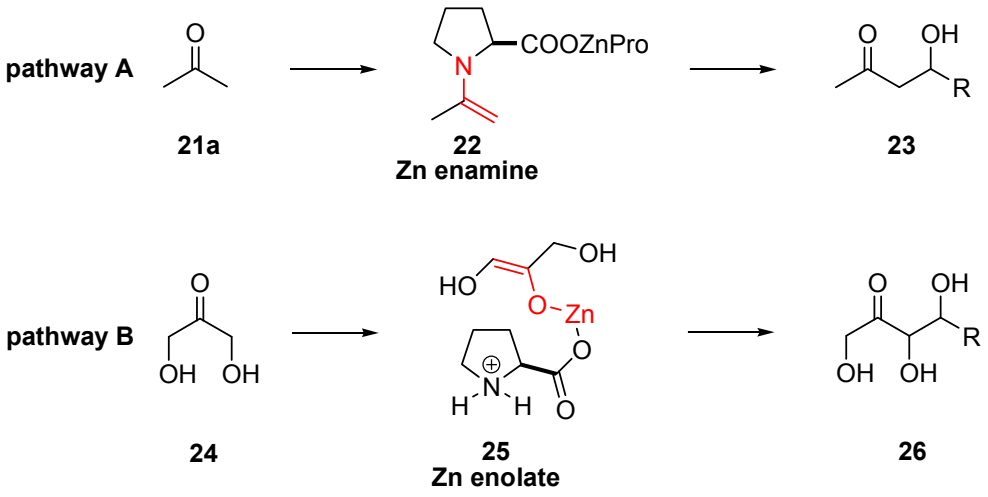



**Figure 2.6** Reymond zinc enolate mechanism

In this study the reaction of acetone with aldehydes in aqueous medium, under catalysis by zinc-proline (Zn(*S*)-$Pro_2$) and secondary amines, had been shown to proceed via the enamine mechanism (pathway A, Figure 2.6). Evidence for that was the

product arising from reductive trapping of the iminium intermediate. On the other hand, the aldol reaction of dihydroxyacetone (**24**), under catalysis by zinc-proline and by general bases such as N-methylmorpholine (NMM) had been shown to occur *via* a rate-limiting deprotonation at the α-carbon and to involve the enolate intermediate (pathway B, Figure 2.6).

In a different mechanism (Figure 2.7), based on Seebach[50] oxazolidinones, the initially formed iminium ion (**27**) equilibrates to the corresponding oxazolidinone (**28**). A Lewis acid (e.g., LiCl) could complex to the Lewis base centers, which are abundantly present in all species involved in the catalytic cycle. Complexation to the carbonyl group of the **28** would facilitate the equilibration to the **27** ion and cause faster formation of the enamine **22a** and, consequently, a more rapid reaction with aldehyde. On the other hand, the Lewis acid could complex to the active sites of **30** facilitating formation of the iminium ion II (**29**) and its hydrolysis to the desired aldol adduct **23**.

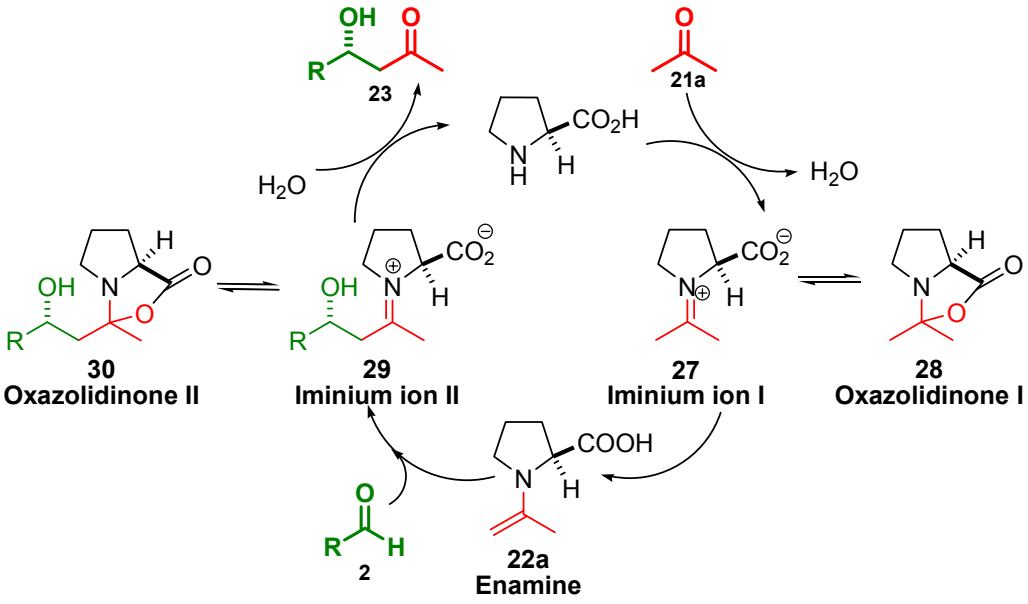
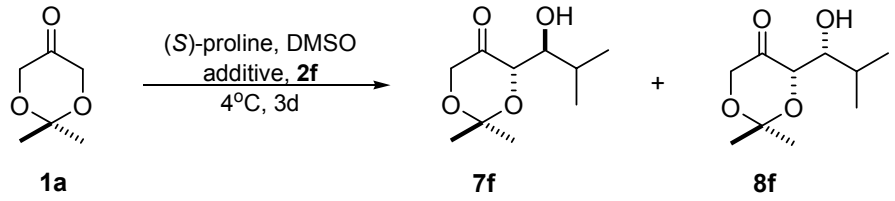



**Figure 2.7** Seebach oxazolidinones in proline catalyzed aldol reaction

Clearly, more research is required to gain further understanding of the details of this operationally simple yet mechanistically complex process.

### 2.3.5 Investigation on the effect of additives in (*S*)-proline catalyzed aldol reaction

In previous section the mechanistic approaches were presented for better understanding of the process. The studies shown below were done to probe that the generality of additives impact on the selectivity in proline catalyzed aldol reaction.




**Scheme 2.12**

**Table 2.5** Effect of additives on selectivity in (*S*)-proline catalyzed aldol reaction of dioxanone **1a** with isobutyraldehyde **2f**

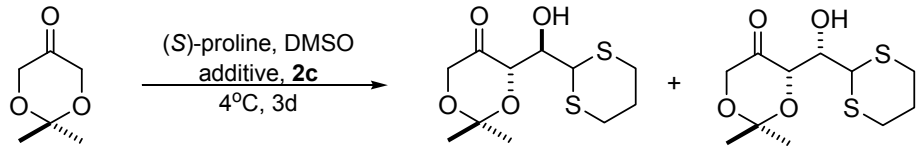
| Entry | Additive (eq) | Isolated yield[a,b] [%] | ee (*anti*)[%] |
|---|---|---|---|
| 1 | - | 65 | 86 |
| 2 | LiCl (1) | 66 | 92 |
| 4 | PPTS (1) | 70 | 96 |
| 5 | LiF (1) | 64 | 98 |
| 6 | LiBr (1) | 51 | 88 |
| 7 | LiI (1) | 47 | 96 |
| 8 | CsCl (1) | 65 | 98 |
| 9 | $CeCl_3$(1) | 43 | 92 |
| 10 | $ZnCl_2$ (1) | 9 | - |
| 11 | $Li_2CO_3$ (1) | 36 | 84 |

[a] The isolated yield refers to the *anti* product [b] The dr of all the reactions were > 99

Addition of weak acids in (*S*)-proline catalyzed aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one (**1a**) and isobutyraldehyde (**2f**) was briefly investigated. The results are summarized on Scheme 2.12 and Table 2.5 and indicated that co-catalysts had minor influence on enantioselectivity in the reaction of **1a** with **2f**. At the same time diastereoselectivity remained very high (> 99). Addition of PPTS, LiF or CsCl enhanced the ee from 86 % (entry 1 no additive) to 96 - 98 % (entry 4,5 and 8). Addition of $ZnCl_2$ to the reaction mixture led to the formation of the desired product in low yield (entry 10). That might have been associated with the opening of the acetal ring caused by strong Lewis acidity of $ZnCl_2$.

### 2.3.6 Effect of additives on selectivity of (*S*)-proline catalyzed aldol reaction of dioxanone with 1,3-dithiane-2-carbaldehyde

Effect of additives on selectivity in (*S*)-proline catalyzed aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one (**1a**) with 1,3-dithiane-2-carbaldehyde (**2c**) was studied (Scheme 2.13). A similar trend in influence of LiCl, PPTS or $H_2O$ on selectivity (enantioselectivity in this case) was observed. In the presence of 1-(*S*)-(+)-10-camphorsulfonic acid (Table 2.6, entry 9) reaction did not work. That might have been due to the relatively high acidity of the additive, which could cause opening of the acetal system of dioxanone.




**Scheme 2.13**

**Table 2.6** Effect of additives on selectivity in (*S*)-proline catalyzed aldol reaction of **1a** with 1,3-dithiane-2-carbaldehyde (**2c**)

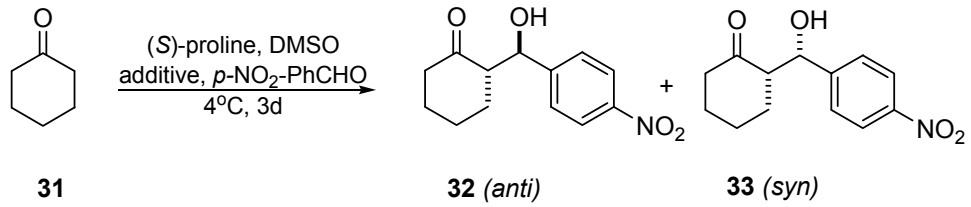
| Entry | Additive (eq) | Isolated yield [%] | dr 8c:7c | er (*anti*)[%] |
|---|---|---|---|---|
| 1 | - | 78 | 2 : 98 | 66 |
| 2 | $H_2O$ (3) | 80 | 2 : 98 | 90 |
| 3 | LiCl (1) | 85 | 2 : 98 | 90 |
| 4 | PPTS (1) | 83 | 2 : 98 | 92 |
| 5 | LiBr (1) | 71 | 2 : 98 | 58 |
| 6 | CsCl (1) | 78 | 2 : 98 | 52 |
| 7 | Phenol (1) | 84 | 2 : 98 | 82 |
| 8 | 2-naphtol (1) | 65 | 2 : 98 | 72 |
| 9 | CSA (1) | - | - | - |
| 10 | *p*-TsOH $H_2O$ (1) | - | - | - |

### 2.3.7 Effect of additives on selectivity in (*S*)-proline catalyzed aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde

Effect of additives on selectivity in a simpler model i.e. (*S*)-proline catalyzed aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde was investigated as well (Scheme 2.14). Yields of the reactions varied from 47 to 83 %. Beneficial influence on selectivity (enantio- and diastereo-) was observed in cases when LiCl, PPTS or $H_2O$ were employed as co-catalysts[42] (Table 2.7).

A literature search indicated that cyclohexanone had been mostly studied as a model system to test new catalysts.[51] A very recent report by Peng described the effectiveness of dipeptides on the selectivity in aldol reaction of cyclohexanone.[52] However, it was shown that the simple aldol reaction with (*S*)-proline proceeded in a moderate yield, diastereo- and enantioselectivity.[53] Addition of co-catalyst, like lithium salts, might be

advantageous so designing of new catalysts to improve selectivities might not be necessary.




**31** **32** *(anti)* **33** *(syn)*

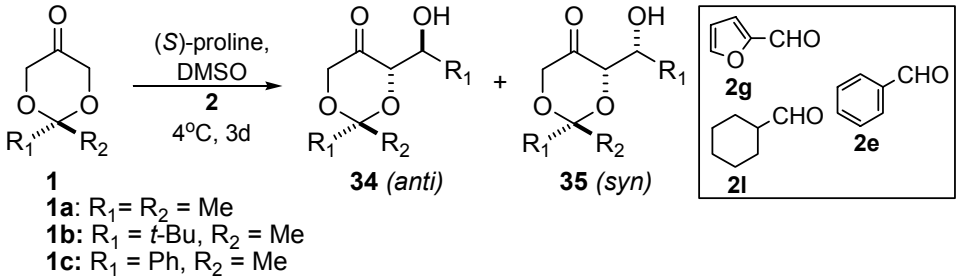
**Scheme 2.14**

**Table 2.7** Effect of additives on selectivity in (*S*)-proline catalyzed aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde

| Entry | Additive (eq) | Isolated Yield [%] | dr *syn* : *anti* | ee (*anti*)[%] |
|---|---|---|---|---|
| 1 | - | 56 | 1 : 2.0 | 64 |
| 2 | $H_2O$ (3) | 79 | 1 : 15.5 | 80 |
| 3 | LiCl (1) | 81 | 1 : 6.1 | 94 |
| 4 | PPTS(1) | 83 | 1 : 15.2 | 80 |
| 5 | LiBr (1) | 65 | 1 : 1.4 | - |
| 6 | LiI (1) | 79 | 1 : 2.1 | 28 |
| 7 | CsCl (1) | 74 | 1 : 2.5 | 74 |
| 8 | $ZnCl_2$ (1) | 72 | 1 : 3.9 | 40 |
| 9 | $Li_2CO_3$ (1) | 47 | 1 : 1.9 | 6 |

### 2.3.8 Investigation on effect of substitution on dioxanone ring on selectivity in (*S*)-proline catalyzed aldol reaction

Next, the effect of substitution on the dioxanone ring was investigated (Scheme 2.15, Table 2.8).




**Scheme 2.15**

**Table 2.8** Effect of substitution on dioxanone ring on selectivity in aldol reaction catalyzed by (*S*)-proline

| Entry | Starting dioxanone | Additive (1eq) | 2 | Time (days) | Yield [%] | dr (*syn*:*anti*) |
|---|---|---|---|---|---|---|
| 1 | $R_1$=$R_2$= Me | - | **2g** | 3 | 19 | 1 : 2 |
| 2 | $R_1$=$R_2$= Me | LiCl | **2g** | 3 | 45 | 1 : 3 |
| 3 | $R_1$= Me, $R_2$= *t*-Bu | - | **2g** | 3 | 35 | 1 : 10 |
| 3 | $R_1$= Me, $R_2$= *t*-Bu | LiCl | **2g** | 3 | 65 | 1 : 13 |
| 4 | $R_1$=$R_2$= Me | - | **2l** | 3 | 80 | 1 : 25 |
| 5 | $R_1$=$R_2$= Me | LiCl | **2l** | 3 | 74 | > 99 |
| 6[a] | $R_1$= Me, $R_2$= Ph | - | **2l** | 3 | 60 | 1 : 5 |
| 7[a] | $R_1$= Me, $R_2$= Ph | LiCl | **2l** | 3 | 65 | 1 : 12 |
| 8 | $R_1$= Me, $R_2$= *t*-Bu | LiCl | **2l** | 4 | 79 | > 99 |
| 9 | $R_1$=$R_2$= Me | - | **2e** | 3 | 54 | 1 : 1.8 |
| 10 | $R_1$=$R_2$= Me | LiCl | **2e** | 3 | 75 | 1 : 2.4 |
| 11[a] | $R_1$= Me, $R_2$= Ph | - | **2e** | 3 | 50 | 1 : 2 |
| 12[a] | $R_1$= Me, $R_2$= Ph | LiCl | **2e** | 4 | 60 | 1 : 3 |
| 13 | $R_1$= Me, $R_2$= *t*-Bu | LiCl | **2e** | 4 | 71 | 1 : 8 |

[a] reactions proceeded in poor reproducibility

Reaction of 2,2-dimethyl-1,3-dioxan-5-one (**1a**) with furan-2-carbaldehyde (**2g**) in the absence of lithium salts not only preceded with low yield, but also gave two isomeric, inseparable by chromatography products, in a 1 : 2 ratio (entry 1). Addition of LiCl (entry 2) improved the yield however diastereoselectivity changed insignificantly. On the other hand, when one of the substituents on the dioxanone ring was changed from methyl to *tert*-butyl, not only the overall yield increased but also diastereoselectivity of the reaction was found to be much higher (entry 3). Since the beneficial effect of additives on selectivity of this type of reactions was already described above. I will not focus on this issue in details; however entries 1, 4, 6, 9 and 11 in Table 2.8 are included for contrast.

A similar trend was observed in other examples. *tert*-Butyl substitution at position 2 of the dioxanone ring had advantageous impact on the selectivity in comparison to the $C_S$ symmetrical dioxanone. The *anti* selectivity increased dramatically from a ratio of 1 : 2 to 1 : 8 in reaction with benzaldehyde as the electrophile (entries 9, 10 and 13). On the other hand, cyclohexanecarbaldehyde (**2l**) used as the acceptor in reaction of **1b** provided the increase in diastereoselectivity from 1 : 25 to 1 : 99 (entries 4 and 8) by changing the substituent in the substrate's acetal fragment. However, in this particular example it was established that high selectivity could be also easily achieved by addition of LiCl to the reaction mixture of ketone **1a** with **2l** (compare entry 4, 5 and 8).

On the other hand, the phenyl group in position 2 on the dioxanone ring had an opposite influence on selectivity. (*S*)-Proline catalyzed aldol reaction of **1c** with aldehyde **2l** gave 1 : 5 mixture of *syn* to *anti* products, which can be compared to 1 : 25 (entries 6 and 4, no additive), or 1 : 12 to 1 : 99 (entries 7 and 5, with LiCl as a co-catalyst). When benzaldehyde (**2e**) was employed as an electrophile the *anti* selectivity increased somewhat from 1 : 2.4 to 1 : 3 (entries 10 and 12), though the reaction was very messy.

### 2.3.9 Conclusions

The effect of additives in (*S*)-proline catalyzed aldol reaction was investigated. Beneficial influence on selectivity was observed when LiCl or PPTS were used as co-catalyst. Other lithium salts, or weak acids had minor or harsh impact on selectivity in organocatalytic aldol reaction. Mechanistically, the role of additives is still unclear and requires more studies.

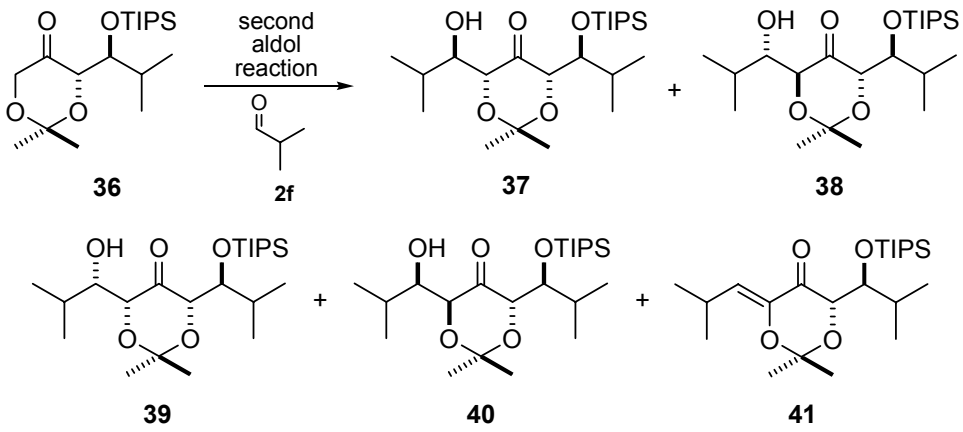
The effect of substitution on dioxanone ring on selectivity in (*S*)-proline catalyzed aldol reaction was investigated. It was found that not only the presence of additives but also substitution on C-2 exert major effects on selectivity and yields. Aliphatic group (*tert*-butyl) was responsible for a large increase of the *anti* selectivity. The aromatic system (phenyl) not only played destructive role in selectivity but also caused the system to be difficult to control (reproducibility).

## 2.4 The second aldol reaction

### 2.4.1 Investigation of the double-aldol formation *via* different enolates

Attempt of the second aldol reaction starting from protected β-hydroxydioxanone derivatives were not successful when organocatalysis was tried. A number of efforts to run the reaction under different conditions (solvent, temperature, reaction times) failed (Scheme 2.16, Table 2.9, entry 1). Diverse catalysts, including (*S*)-prolinethioamides reported by Gryko[54] to promote the bis aldol reaction, were synthesized and applied, however without positive results. Probably, the unsuccessful organocatalytic approach should not be surprising, as the product functionalized at α,α'- positions of the dioxanone was not observed in the reaction run under standard proline catalyzed conditions.

Reactions involving titanium enolate (entry 2) or magnesium enolate (entry 3) of compound **36** afforded only small amounts of dehydrated double aldol **41.** Aluminum enolate chemistry (entry 4) was investigated as an example of the procedure which might give the bis aldol product.[55] However, the experiment did not work, even though a simple reaction between dioxanone and an excess of isobutyraldehyde showed the formation of the unsaturated product in 77 % yield. Experiments involving boron enolates (entry 5) gave, as had already been reported,[26, 27, 56-58] predominantly the *anti-trans-anti* isomer of the double aldol product (**38**) with good selectivity and in 96 % yield. It is worth mentioning that only three of the four possible aldols were observed within NMR detection limit. However, boron enolates did not work well with aldehyde building blocks that contained sulfur moieties (oxidation of sulfur under oxidative workup) and this limitation turn into the boron enolate method being a not reasonable choice in our synthetic objectives, especially in those which involved sulfur atoms in the structure. At this stage the lithium enolate chemistry was proposed (entry 6) as it was already known to be the most versatile and commonly used in organic chemistry for functionalization of the α-position of ketones.[46]




**Scheme 2.16**

**Table 2.9** Aldol addition reaction of compound **36** with isobutyraldehyde (**2f**)

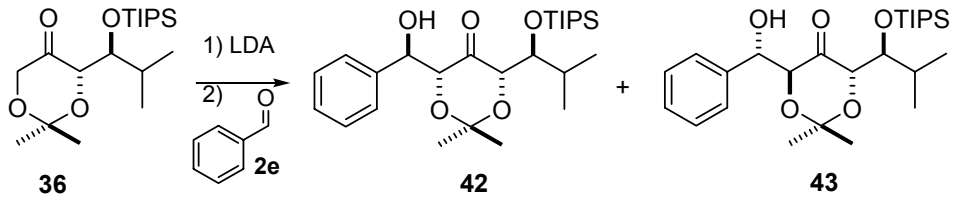
| Entry | Conditions | Products ratio | Yield [%][a] |
|---|---|---|---|
| 1 | Organocatalysis | - | - |
| 2[b] | $TiCl_4$, $(i\text{-Pr})_2EtN$, THF | **41** only | 5 |
| 3[c] | $MgI_2$, $(i\text{-Pr})_2EtN$, DCM | **41** only | 15 |
| 4[d] | $Al_2O_3$,DCM | - | - |
| 5[e] | $Chx_2BCl$, $Et_3N$, $Et_2O$ | **37** : **38 :** (**39** + **40**) 13 : 86 : 1 | 96[f] |
| 6[g] | LDA, THF | **37** : **38 :** (**39** + **40**) 65 : 35 : 0 | 74[f] |

[a] isolated yield, [b] procedure taken from ref.[59] [c] procedure taken from ref.[60] [d] procedure taken from ref.[55] [e] procedure taken from ref.[27] [f] related to combined yield of all isolated isomers

## 2.5 Lithium mediated second aldol reaction

### 2.5.1 Optimization of the reaction conditions

Initially the attempts to generate the lithium enolate from a protected aldol and subjecting it to a reaction with the aldehyde did not look promising. Nonetheless by the optimization of reaction conditions I was able to establish that the reaction worked well if excess of the base and an excess of the aldehyde were used (Scheme 2.17, Table 2.10).




**36** **42** **43**

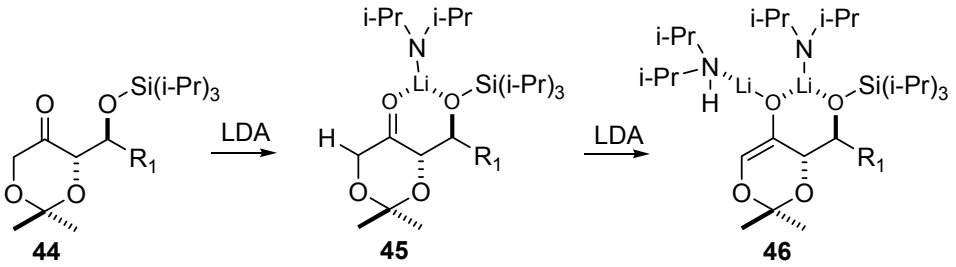
**Scheme 2.17**

**Table 2.10** Aldol reaction of lithium enolate of **36** with benzaldehyde **(2e)**

| Entry | LDA (eq) | 2e (eq) | 42 : 43 | Yield [%] |
|---|---|---|---|---|
| 1 | 1.1 | 1 | 2.7 : 1 | 9 |
| 2 | 2.2 | 1 | 1.9 : 1 | 14 |
| 3 | 3.3 | 1 | 1.8 : 1 | 10 |
| 4 | 1.1 | 3 | - | - |
| 5 | 2.2 | 3 | 8 : 1 | > 90 |
| 6 | 3.3 | 3 | 7.3 : 1 | > 90 |

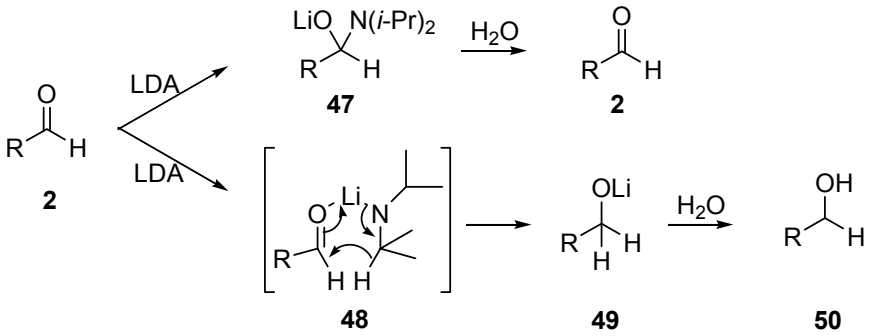
Most likely the first equivalent of the base was complexed to the Lewis basic centers in the substrate and did not take part in deprotonation process. That would be in agreement with the experimental data since more then 1 equivalent of LDA was

required for enolization of protected dioxanone aldols. Presumably the first molecule of the lithium base remains complexed to the substrate (Scheme 2.18, structure **45**). The second equivalent of the base is needed for the enolization (structure **46**).




**Scheme 2.18**

Upon addition of the aldehyde the first molar equivalent of the aldehyde was consumed in the addition reaction with LDA, as expected.[61] The schematic representation of this process on the simple aldehyde, is depicted in Scheme 2.19

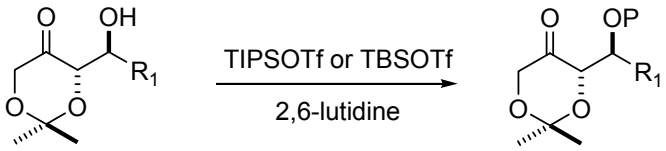



**Scheme 2.19**

### 2.5.2 Aldol reaction of protected β-hydroxydioxanones with different aldehydes

Further in my investigations I used 2.2 – 3.3 equivalents of LDA since these amounts of the base gave the most optimal results. I examined a number of sequential processes in which the first aldol reaction was done under organocatalytic conditions established in our laboratory[42] (proline, additive, DMSO, 4 °C, 1 - 4 days). Then the

aldol product was purified and protected as the corresponding TIPS or TBS ether. The protection proceeded easily in up to 97 % overall yield (Scheme 2.20, Table 2.11).




**7** **51**

P = TIPS or TBS

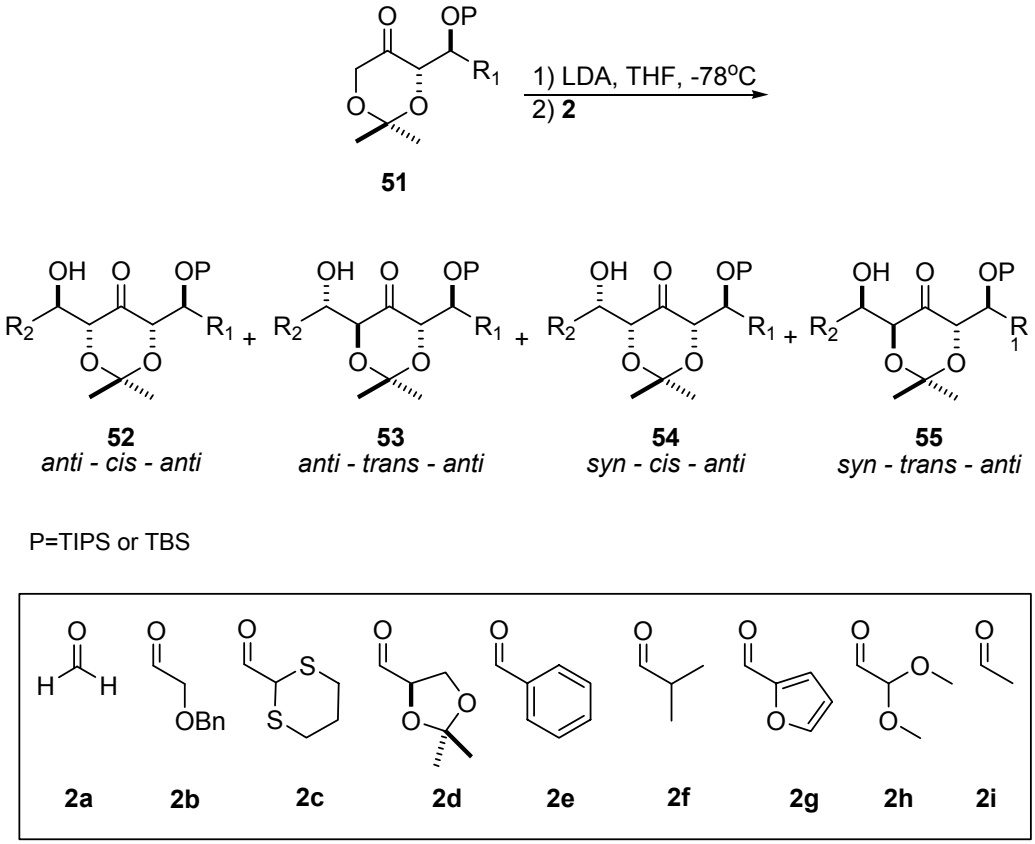
**Scheme 2.20**

**Table 2.11** Protection of **7** as TIPS or TBS ether

| Entry | Method[a] | $R_1$ | P | Yield [%][b] |
|---|---|---|---|---|
| 1 | A | *i*-Pr | TIPS | 90 |
| 2 | B | *i*-Pr | TBS | 91 |
| 3 | A | Ph | TIPS | 82 |
| 4 | A |  | TIPS | 96 |
| 5 | B | | TBS | 95 |
| 6 | A |  | TIPS | 97 |
| 7 | B | | TBS | 93 |
| 8 | A |  | TIPS | 82 (58)[c] |
| 9 | A |  | TIPS | 95 |

[a] Method A: 2,6-lutidine (2.0 eq), TIPSOTf (1.2 - 1.5 eq), THF, 0 °C - rt, Method B: 2,6-lutidine (2.0 eq), TBSOTf (1.2 - 1.5 eq), THF, -78 °C, [b] Isolated yield after chromatography column on silica, [c] Product was protected *in situ* after (*S*)-proline catalyzed aldol reaction – yield over two steps

After protection, the products were subjected to enolization with LDA (2.2 – 3.3 equivalents, THF, -78 °C), followed by addition of the aldehyde. Having elaborated the conditions for the second aldol reaction *via* lithium enolates I could now investigate a number of examples with the aim of employing them later in synthesis of sugars or other polyoxygenated products. The results of those studies are shown in general Scheme 2.21 and Table 2.12.




**Scheme 2.21**

**Table 2.12** Lithium amide mediated aldol reaction of **51** with **2**

| Entry | P | $R_1CHO$ | $R_2CHO$ | 52 : 53 : (54 + 55) | 52 : 53 | Yield [%] |
|---|---|---|---|---|---|---|
| 1 | TBS | **2f** | **2f** | 63 : 37 : 0 | 1.7 : 1 | 51 (68)[a] |
| 2 | TIPS | **2f** | **2f** | 66 : 34 : 0 | 1.9 : 1 | 77 |
| 3 | TIPS | **2f** | **2e** | 76 : 14 : 10 | 5.4 : 1 | 99 |
| 4 | TIPS | **2f** | **4c** | 86 : 13 : 1 | 6.6 : 1 | 67 (74)[a] |
| 5 | TIPS | **2h** | **2f** | 64 : 27 : 9 | 2.4 : 1 | 54 |
| 6 | TBS | **2h** | **2e** | 64 : 34 : 2 | 1.9 : 1 | 75 |
| 7 | TIPS | **2e** | **2c** | 63 : 34 : 3 | 1.8 : 1 | 86 |
| 8 | TIPS | **2h** | **2a** | 70 : 30 : 0 | 2.3 : 1 | 29 (39)[a] |
| 9 | TBS | **2h** | **2i** | 83 : 17 : 0 | 4.9 : 1 | 79 (81)[a] |
| 10 | TBS | **2h** | **2c** | 91 : 9 : 0 | 10 : 1 | 86 (97)[a] |
| 11 | TIPS | **2h** | **2c** | 74 : 26 : 0 | 2.8 : 1 | 88 |
| 12 | TIPS | **2h** | **2b** | 56 : 44 : 0 | 1.3 : 1 | 71 |
| 13 | TIPS | **2h** | **2d** | 78 : 22 : 0 | 3.5 : 1 | 45 (79)[a] |
| 14 | TBS | **2h** | **2d** | 86 : 14 : 0 | 6.1 : 1 | 76 (85)[a] |
| 15 | TBS | **2h** | **2g** | 79 : 18 : 3 | 4.4 : 1 | 91[b] |
| 16 | TBS | **2d** | **2c** | 91 : 9 : 0 | 10 : 1 | 67 (81)[a,b] |
| 17 | TBS | **2d** | **2d** | 98 : 2 : 0 | 49 : 1 | 83 (> 99)[a] |

[a] yield calculated based on recovered starting material (BORSM), [b] in addition to desired products α,β-unsaturated ketone was isolated in 9 % yield

Aldol reaction of α-substituted dioxanones preceded well with an excess of lithium base. In most of the cases only two out of four possible products were detected by NMR (Scheme 2.21, Table 2.12, entries 1, 2, 8, 9, 10, 11, 12, 13, 14, 16, 17). Selectivities depended on the nucleophile as well as the electrophile used and varied from 1.7 : 1 to 10 : 1 *anti–cis–anti* to *anti–trans–anti* isomers. The aldehyde which rendered the highest π - stereofacial outcome was 1,3-dithiane-2-carbaldehyde (**2c**) that provided the aldol adducts in selective fashion (entries 10, 16). As it was described in the case of aldol reaction on unmodified dioxanone β-substituted aldehyde exerted the lowest selectivity among all aldehydes used furnishing the mixture of disubstituted dioxanones in nearly equimolar ratio (entry 14). In most of the examples presented in the table TBS protected staring materials provided the final products in higher selectivieties then those that were derived from β-hydroxyketones protected with TIPS (compare entries 10 and 11, 13 and 14). That might be related to steric preferences in the transition state, which clearly tolerated *tert*-butyl–dimethyl system better than the three large *iso*-propyl groups. Remarkable was the case in entry 8. In our studies with dioxanones we had never been able to accomplish a reaction with formaldehyde, despite trying a number of different conditions including organocatalysis. Though the selectivity and yield of these reactions were low, this was the first example of the direct introducing the formyl group onto dioxanone by using lithium enolate chemistry.

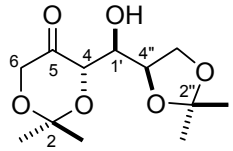
While the level of diastereoselectivity clearly could be improved, the simplicity of this approach compensated for less than ideal distribution of isomeric products. It should be noted that a number of isolated aldol *anti-cis-anti* products consist of the complete carbon skeleton of carbohydrates and have the necessary oxygen functional groups in the right positions. Thus, easy to envisage functional group manipulations of these compounds (reduction-deprotection sequences) offer access to hexoses, mostly 6-C-substituted (entries 4 - 9), heptoses (entries 10 - 12), octoses (entries 13, 14, 16) and nonoses (entry 17).

## 2.6 Stereochemistry issues

### 2.6.1 Stereochemistry in the "first aldol" reaction

During the synthesis an important consideration was the assignment of relative and/or absolute stereochemistry. That was also in the case in solving of the structure of the newly synthesized compounds, which had proven to be a non-trivial task. Many natural products contain l,3-diols, and determining the stereochemistry of these diols and polyols can be very challenging.

The stereochemistry in the first aldol was solved by comparison of the data obtained by lithium amide mediated aldol reaction of dioxanone and (*R*)-glyceraldehyde by Nowak[21] with the data obtained in (*S*)-proline catalyzed aldol reaction. The choice of compound **7d** (Figure 2.8) for comparing the stereochemistry was dictated by the fact that ultimately the assignment of the relative and the absolute configuration of that compound were accomplished by the chemical correlation method with the commercially available sugar – D-tagatose[21] (see Chapter 1 for details).




**7d**

**Figure 2.8** Structure of protected D-tagatose.

In both cases the product of interest was obtained as a white solid with the melting point in approximately the same range (103-105 °C versus 102-103 °C). Comparison of the chemical shifts, splitting patterns and coupling constants values in $^{1}$H NMR and chemical shift in $^{13}$C NMR (in the case of lithium base mediated aldol reaction some of the information were not described in detail by author,[21] however the original spectra were found and the inspection of data was possible), led to the conclusion that in both processes the same isomer was formed as the major product (Table 2.13).

**Table 2.13** Comparison of physical properties and spectral data of **7d** obtained in different processes

| | | **Lithium amide mediated aldol reaction**[a,b] | **(*S*)-proline catalyzed aldol reaction**[c] |
|---|---|---|---|
| **appearance** | | white solid | white solid |
| **mp (° C)** | | 103-105 | 102-103 |
| **$[\alpha]_D$** | | **$[\alpha]_D$** $^{25}$ -167 (c 1.1, $CHCl_3$) | **$[\alpha]_D$** $^{24}$ -148 (c 0.9, $CHCl_3$) |
| **$^1$H NMR ($\delta$ ppm $C_6D_6$)** | **CH-C4** | 4.25-4.32, m | 4.30, dd, *J* 1.2, 7.6 Hz |
| | **CH-C1'** | 3.65, m | 3.67, ddd, *J* 3.3, 3.3, 7.6 Hz |
| | **CH-C4"** | 4.25-4.32, m | 4.28 ddd *J* 3.3, 6.8, 7.5 Hz |
| **$^{13}$C NMR ($\delta$ ppm $CDCl_3$)** | **C5** | 210.4 | 210.5 |
| | **C4** | 73.5 | 73.7 |
| | **C1'** | 70.1 | 70.3 |
| | **C4"** | 75.2 | 75.4 |
| | **C2** | 101.3 | 101.5 |

[a] data from ref. [21], [b] NMR data was obtained on a Bruker AM-300 (300 MHz), [c] NMR data was obtained on Bruker 500 (500 MHz)

### 2.6.2 Stereochemistry in the "second aldol" reaction

The stereochemistry problem in second aldol reaction was more complicated to solve. The reaction of lithium enolate of β-protected hydroxyketone **56** theoretically might give rise to four isomeric products: *anti–cis–anti*, *anti–trans–anti*, *syn-cis–anti* and *syn–trans–anti* (as shown in Scheme 2.21). Prediction of the major component of this reaction could be based on some literature precedents,[62] however to fully support the stereochemistry outcome from this type of reaction some experiments were proposed. The general overview is depicted in the Figure 2. 9.

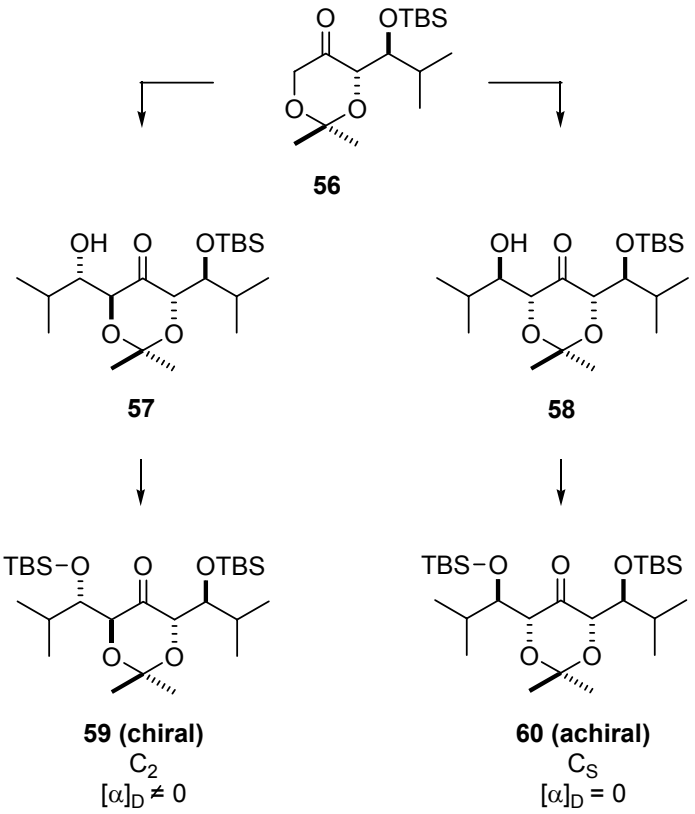
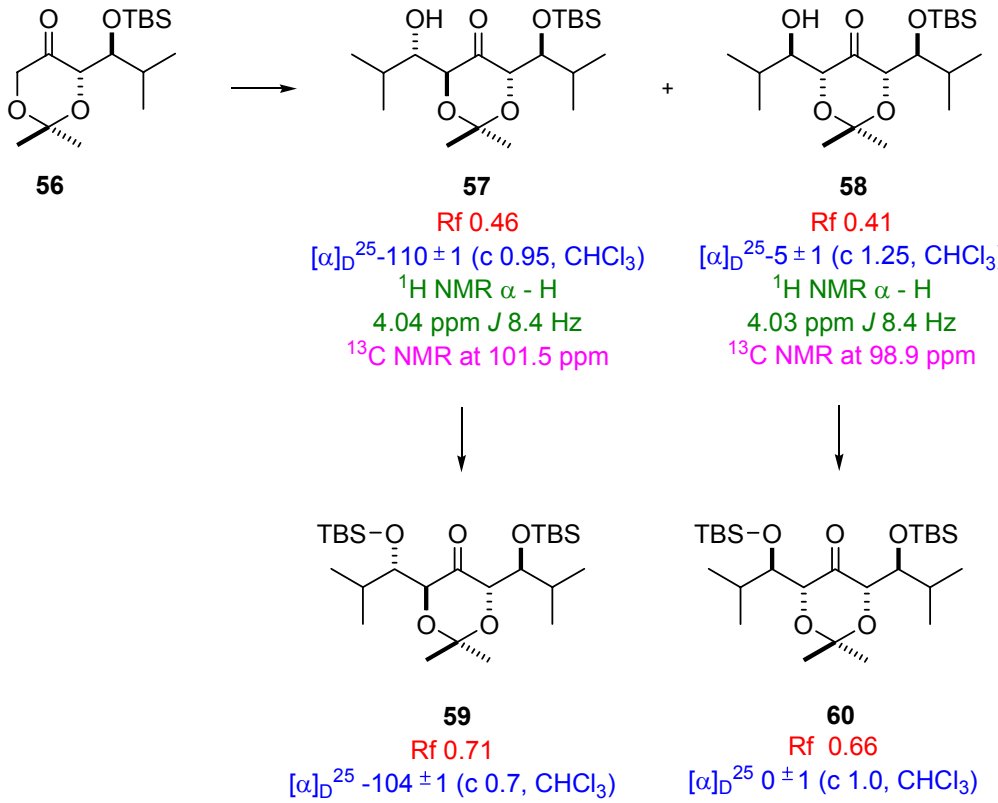



**Figure 2.9** Schematic representations of experiments for solving the stereochemistry problem in the "second aldol" reaction

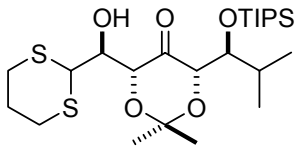
TBS protected aldol product **56** was subjected for enolization and sequential second aldol reaction with isobutyraldehyde as the electrophile. The presence of two signals in $^{1}$H NMR at 4.04 ppm (dd, *J* 8.4 Hz) and 4.03 ppm (dd, *J* 8.4 Hz) designated the formation of two products with *anti* relative configuration around a newly created

bond. Also inspection of the $^{13}C$ NMR spectra run on a crude reaction mixture and integration of characteristic peaks at 98.9 and 101.5 ppm indicated the formation of two isomeric product in 1.7 : 1 ratio. The $[\alpha]_D$ of the major component of the mixture had a value of -5 (in chloroform), on the other hand, the isomer formed in lower yield, rotated the plane of polarized light by -110 (in chloroform). Protection of the hydroxyl group of each of the isolated isomers with TBSOTf in the presence of 2,6-lutidine in THF at -78 °C after 1 h gave the products, which, after purification by SCC (short column chromatography), provided the pure compounds. Once again, the optical rotation was measured in chloroform and was found to be 0 ± 1 for the major isomer and -104 ± 1 for the minor one. That test led to the conclusion that the main component of the reaction of **56** with isobutyraldehyde, after protection, was achiral (belonged to the $C_S$ symmetry point group) and did not show optical activity. The second, less polar component of the reaction mixture, formed in lower yield, after protection as TBS ether showed the optical rotation value of -104 ± 1 that clearly indicated lower symmetry. Summary of the data is presented in Scheme 2.22.




**Scheme 2.22**

As an additional test of the stereochemistry of the product of the second aldol reaction an effort was made to obtain a crystalline sample for X-ray analysis. One of the bis aldol products **52fc** was a white solid and provided a crystal suitable for crystallography. The structure of the crystallized compound and the ortep drawing are shown in Figure 2.10.




**52fc**

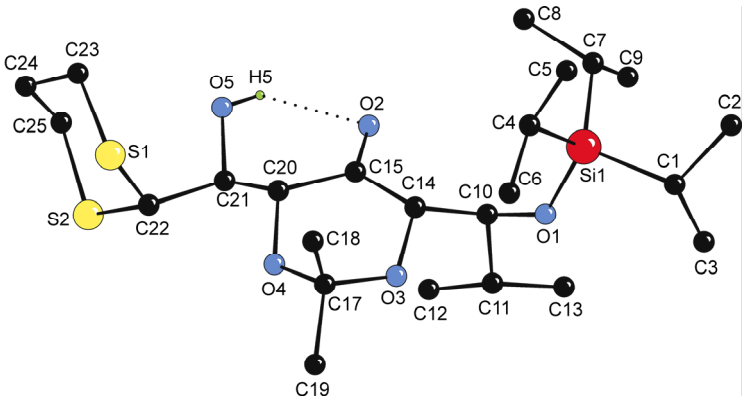



**Figure 2.10** Ortep diagram for compound **52fc**

Solving the problems related to the stereochemistry of newly formed products in each of the second aldol reaction was quite a challenge. Some general observations, such as that the stereoselectivity favoured the *anti-cis-anti* isomer over the *anti-trans-anti* isomer were apparent, but still the question remained whether all the cases followed this trend. Careful inspection of the $^{1}$H NMR spectra was inconclusive as the coupling constant values (*J*) could not be taken for granted as the sufficient source for establishing the stereochemistry. The chemical shifts varied, but the differences depended mostly on the nature of substituents, perhaps more so then on the relative

configuration. Moreover, in some of the cases the NMR peaks were overlapping, so even though a common tendency was observed, the data could not be used for evaluating the stereochemistry securely enough. However, the inspection of the $^{13}C$ NMR proved to be helpful, as a general trend was observed. Summary of this study is outlined in Figure 2.11 and Table 2.14.

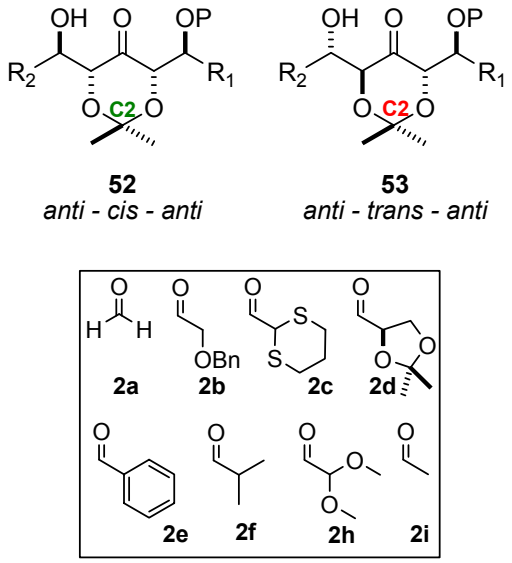



**Figure 2.11** General structures of **52** and **53** used in $^{13}C$ NMR studied

It was established that the chemical shifts of the acetal carbon atom from the dioxanone ring in all the compounds having substituents at the α and the α'-positions on the same side of the ring e.g., being *cis* to each other (structure **52** in Figure 2.11), were in the range of 98.7 – 99.1 ppm. On the other hand, aldol adducts with the *trans* configuration of the substituent's next to the carbonyl group (structure **53** in Figure 2.11) had the quaternary carbon at C-2 in 2,2-dimetyl substituted dioxanone in the range of 101.1 – 102.0 ppm. Those results were consistent with those observed and reported by Heathcock on simpler aldol products.[63] Moreover the outcome from my studies showed some similarity to data published by Rychnovsky, who observed a similar trend in a series of *cis* and *trans* substituted 1,3-dioxanes.[64]

**Table 2.14** Comparison of chemical shift of **52** and **53** at C-2 in $^{13}C$ NMR

| Entry | P | $R_1CHO$ | $R_2CHO$ | C-2 of 52 δ: $^{13}C$ NMR [ppm] | C-2 of 53 δ: $^{13}C$ NMR [ppm] |
|---|---|---|---|---|---|
| 1 | TBS | **2f** | **2f** | 98.9 | 101.5 |
| 2 | TIPS | **2f** | **2e** | 98.9 | 101.8 |
| 3 | TIPS | **2f** | **2c** | 99.1 | 101.8 |
| 4 | TIPS | **2e** | **2c** | 99.1 | 101.9 |
| 5 | TBS | **2h** | **2c** | 98.9 | 101.9 |
| 6 | TIPS | **2h** | **2c** | -[a] | 102.0 |
| 7 | TIPS | **2h** | **2d** | 98.9 | 101.9 |
| 8 | TBS | **2h** | **2d** | 99.0 | -[a] |
| 9 | TBS | **2h** | **2e** | 98.7 | 101.7 |
| 10 | TIPS | **2h** | **2a** | 98.7 | 101.6 |
| 11 | TIPS | **2h** | **2b** | 98.7 | -[a] |
| 12 | TBS | **2h** | **2i** | 98.7 | 101.5 |
| 13 | TBS | **2d** | **2c** | 99.1 | 101.1 |

[a] at the time these studies were performed sample was unavailable for measurement due to its further transformation or decomposition

This trend was also maintained for the bis aldols products synthesized on the 2-*tert*-butyl-2-methyl-1,3-dioxan-5-on (**1b**) building block. The carbon at C-2 of the *anti-trans-anti* aldols kept the tendency to appear downfield in comparison to the *anti-cis-anti* compounds. Results are shown in Figure 2.12 and Table 2.15.

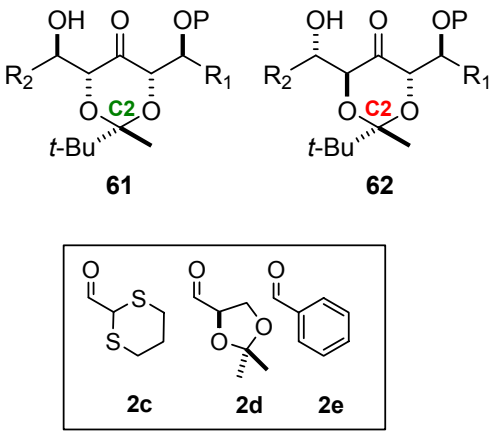



**Figure 2.12** General structures of **61** and **62** used in $^{13}C$ NMR studies

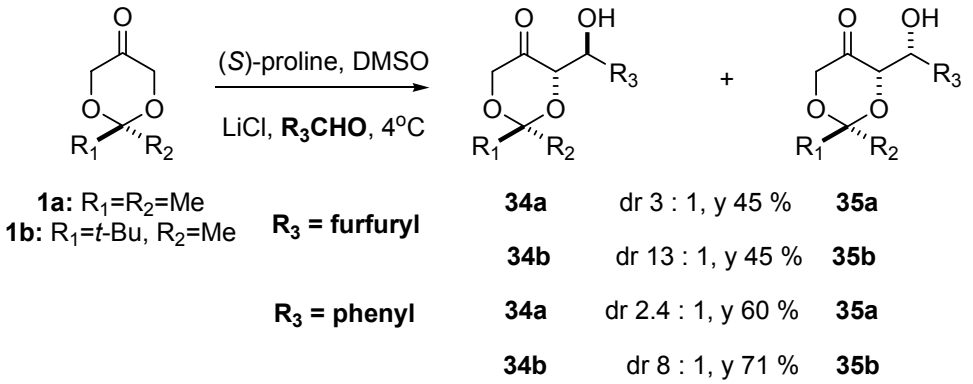
**Table 2.15** Comparison of the chemical shift of **61** and **62** at C-2 in $^{13}C$ NMR

| Entry | P | $R_1$ | $R_2CHO$ | C-2 of 61 δ: $^{13}C$ NMR [ppm] | C-2 of 62 δ: $^{13}C$ NMR [ppm] |
|---|---|---|---|---|---|
| 1 | TIPS | ***i*-Pr** | **2c** | 102.8 | -[a] |
| 2 | TIPS | ***i*-Pr** | **2e** | 102.9 | 106.2 |
| 3 | TIPS | **Ph** | **2d** | 102.8 | 105.8 |

[a] only one isomer was isolated from the reaction mixture

## 2.7 Investigation on improving the selectivity in the "second aldol" reaction

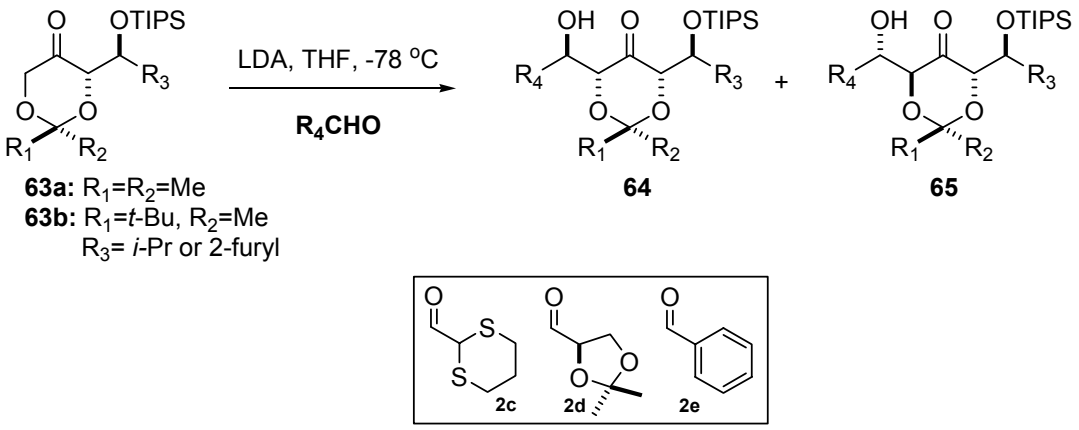
In the section 2.3.7 the investigation of the effect of substitution on the dioxanone ring on the selectivity of the (*S*)-proline catalyzed aldol reactions was described. It was observed that a large substituent (*tert*-butyl) at the acetal position of the dioxanone ring significantly increased selectivity. Summary of this study is presented in Scheme 2.23.




**Scheme 2.23**

While 2,2-dimethyl substituted dioxanone **1a** gave rise to two isomeric compounds in a 1 : 3 ratio in the presence of lithium chloride as an additive, 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one (**1b**) provided the mixture of *syn* and *anti* aldol adducts in the 1 : 13 ratio under the same reaction conditions when furan-2-carbaldehyde was used as the electrophile. Analogous situation was observed when benzaldehyde was used as the acceptor. The diastereoselectivity (*syn* to *anti*) increased from 1 : 2.4 to 1 : 8 and the yield increased from 60 to 71 %.

Having this result in hand, it was decided to inspect whether the second aldol reaction would also proceed in a higher selectivity with the *tert*-butyl substituted starting material. The results are shown in Scheme 2.24 and Table 2.16.




Scheme 2.24

**Table 2.16** Comparison of the selectivity in the "second aldol" reaction of differently protected dioxanones

| Entry | Ketone | $R_3$ | $R_4$ CHO | 64 : 65 | Yield |
|---|---|---|---|---|---|
| 1 | 63a | *i*-Pr | **2c** | 6.6 : 1 | 67 (74)[a] |
| 2[b] | 63b | *i*-Pr | **2c** | 3.3 : 1 | 57[c] |
| 3 | 63a | *i*-Pr | **2e** | 5.4 : 1 | 99 |
| 4[b] | 63b | *i*-Pr | **2e** | 3.1 : 1 | 71[c] |
| 5 | 63b | 2-furyl | **2d** | 1 : 4.9 | 42[d] (57)[a] |

[a] yield calculated based on recovered starting material (BORSM), [b] data from ref. [65], [c] isolated yield refers to the major isomer [d] in addition to desired products, the α,β-unsaturated ketone was isolated in 26 % yield

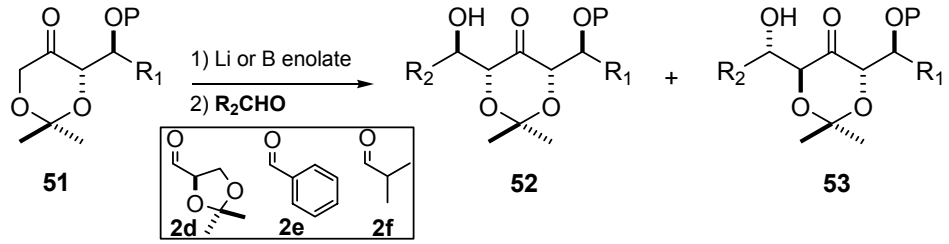
Diastereoselectivity varied depending on the substituent at C-2 position in the starting dioxanone. Contrary to the results observed in the "first aldol" reaction promoted by (*S*)-proline, the second aldol gave lower diastereoisomer ratio. In the case of aldehyde **2c** the selectivity dropped from 6.6 : 1 to 3.3 : 1 (compare entries 1 and 2 in Table 2.16). The same trend was observed when benzaldehyde was employed as the electrophile: the diastereomeric ratio changed from 5.4 : 1 to 3.1 : 1 (entries 3 and 4). One could expect to observe a beneficial influence of the *tert*-butyl group on the dioxanone ring, however

better selectivities were achieved when 2,2-dimethyl substituted ketone **63a** was the starting material. That seemed to signal that the nature of the transition state involved in the "second aldol" reaction is strongly depended on the substitution at C-2 position. While methyl groups on the dioxanone lead to moderate selectivieties, larger groups, like *tert*-Bu might play destructive role in π-facial recognition by the electrophile.

An interesting observation was made when aldol **63b,** with the furan ring as a ligand $R_3$, was subjected to second aldol reaction with (*R*)-glyceraldehyde (**2d**) under standard condition with LDA. The opposite selectivity was noted, leading to the product **65b** as the major isomer in the reaction mixture. The reaction proceeded in low yield of 42 %, however the starting material was recovered (28 %) as well, and the product of the aldol condensation (α,β-unsaturated ketone) was formed in 26 %. Since this result was unexpected, the probability of epimerization on α stereogenic center was considered. A similar experiment on **63a** couldn't be undertaken, since there were no methods to obtain this starting material in the isomerically pure form. As it was mentioned previously (see section 2.3.7 for details), the organocatalytic experiment afforded only the inseparable mixture of the *anti* and *syn* products in 3 : 1 ratio and in 45 % yield in the presence of additive. However another method involving boron enolate chemistry was used to rule out the eventual epimerization aspect. As it was already observed during the initial investigation of the double-aldol formation via different enolates (see section 2.5.1) boron enolate chemistry provided opposite stereochemistry then the lithium mediated aldol reaction. In the former case $Chx_2BCl$ was used as the source of boron to form the corresponding enolate of **63b** in the presence of a tertiary amine. Trapping with **2d** provided **64b** and **65b** in a 1 : 3 ratio and 77 % overall yield. Careful analysis of the NMR data together with the $R_f$ and optical rotation values led to the conclusions that in both processes, lithium and boron mediated aldol reaction the same compound **65b** was formed as the major product. This behaviour contrasted with previously observed tendency for boron enolates to give a *trans* bis aldols and lithium enolates to give *cis* bis aldols. The reason might be the transition state which in this case favours the axial attack of the glyceraldehyde over the equatorial attack.

## 2.8 Boron enolate mediated aldol reaction

In the previous section, which deals with the methods for the second aldol reaction, I briefly commented on the boron enolate chemistry being not suitable for our synthetic plan. It should be noted that the strategy involved the oxidative cleavage, and, if my intermediates contained the dithiane moiety, it probably was oxidized to the corresponding sulfoxides. However, the boron enolate method was interesting since the opposite selectivity to the lithium enolate method was observed. For comparison, some of the results from boron and lithium mediated aldol reactions of **51** with **2** are presented in Scheme 2.25 and Table 2.17.




**Scheme 2.25**

**Table 2.17** Aldol addition reaction of compound **51** with **2**

| Entry | Conditions | $R_1$ | $R_2$ CHO | 52 : 53 | Yield[c] |
|---|---|---|---|---|---|
| 1[a] | LDA, THF, -78 °C | *i*-Pr | **2f** | 1.9 : 1 | 77 |
| 2[ad] | $Chx_2BCl$, $Et_3N$, 0°C | *i*-Pr | **2f** | 1 : 7.4 | 82 |
| 3[ae] | $Chx_2BCl$, $Et_3N$, -78 °C | *i*-Pr | **2f** | 1 : 6.6 | 96 |
| 4[b] | LDA, THF, -78 °C | $CH(OMe)_2$ | **2e** | 1.8 : 1 | 75 |
| 5[bd] | $Chx_2BCl$, $Et_3N$, 0 °C | $CH(OMe)_2$ | **2e** | 1 : 12 | 70[c] |
| 6[a] | LDA, THF, -78 °C | $CH(OMe)_2$ | **2d** | 3.5 : 1 | 45(78)[f] |
| 7[a] | $Chx_2BCl$, $Et_3N$, 0 °C | $CH(OMe)_2$ | **2d** | 1 : 8.1 | 78 |

[a] TIPS protected ketone used as a starting material, [b] TBS protected ketone used as a starting material, [c] combined yield of isolated isomers, [d] reaction run in $CH_2Cl_2$ as the solvent, [e] reaction run in $Et_2O$, [f] yield based on recovered starting material

Boron chemistry gave a higher diastereoisomer ratio in comparison to lithium base mediated aldol reactions of **51**. Thus, when an α-substituted aliphatic aldehyde was used as the acceptor the selectivity was found to be 1.9 : 1 and the yield 77 % in the lithium base mediated aldol reaction (entry 1). On the other hand, boron enolate chemistry gave the aldol adducts in the 1 : 7.3 ratio and 82 % yield (entry 2). An aromatic aldehyde as the electrophile provided bis aldol products in 1.8 : 1 dr and 75 % yield when LDA was used as a base (entry 4), but $Chx_2BCl$ furnished the mixture of the corresponding bis aldols in 70 % yield and the ratio to 1 : 12 (entry 5). When (*R*)-glyceraldehyde (**2d**) was used as the acceptor the *anti–cis–anti* versus *anti–trans–anti* selectivity increased significantly (from 3.5 : 1 to 1 : 8.1) when boron chemistry was employed (entries 6 and 7). Furthermore, I found that small changes in the reaction conditions (solvent and temperature) for boron enolate protocol led to insignificant variation in diastereoisomeric ratio of **52** : **53** from 1 : 7.4 to 1 : 6.6 (entries 2 and 3), albeit the excellent yield of 96 % was observed when ether was used as a solvent.

### 2.8.1 Rationalizing of stereochemical outcome

The unexpected selectivity resulting from the equatorial attack on lithium enolates, contrasted sharply with the axial approach of electrophiles in boron enolate chemistry, was interesting. In both studied cases the kinetically controlled aldol reactions should favour axial attack, according to well established models.[66, 67] The stereoelectronic preference for axial attack on cyclic enolates had been rationalized as follows: the preference for the proton abstraction from the axial position rather then the equatorial one in cyclic ketones was discussed by Corey[66] who observed this trend in steroid systems. This observation was rationalized not by steric effects but on the basis of a stereoelectronic argument.[67] It was proposed that the interaction of the π orbital of the C=O bond with the antibonding orbital $\sigma^*$ of the axial C-H bond is responsible for lower strength of that bond. Similar interaction is not possible for the equatorial C-H because of different relative spatial arrangements of the corresponding orbitals (Figure 2.13).

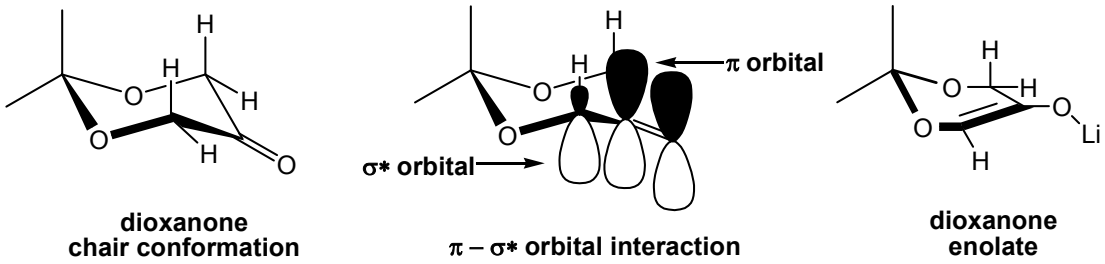



**Figure 2.13** Dioxanone in chair conformation, dioxanone enolate and π - $\sigma^*$ orbital interactions favouring abstraction of the axial proton during deprotonation

The reverse process, i.e., the axial attack was rationalized based on the Valence Bond Theory and especially on the assumption that the principle of microscopic reversibility applies. The same elements of control that acted on deprotonation are present in the reverse process, and thus the addition of electrophiles should favour the axial attack.

Unexpectedly, in the chemistry of dioxanones i.e., in organocatalytic aldol reaction as well as in lithium enolate - mediated aldol, the predominant formation of the products resulted from the equatorial attack. The reasons for such behaviour remain unclear, but it should be noted that similar phenomena were already noticed by Nowak while studying enantioselective deprotonation of dioxanones.[21]

In the boron enolate case the major aldol adduct which was forming, could possibly come from the transition state **66a** (Figure 2.14). The large substituent at the α-position of the dioxanone ring had caused a steric hindrance with the ligands on boron. The electrophile can only approach the bond π of the enolate from its *re* face, without causing additional steric interactions. Assuming that the reaction proceeds through the Zimmerman – Traxler[68] chair-like transition state the major isomer from this process would be **53** having the trans configuration with respect to the substituents at the α and α' position (Figure 2.13).

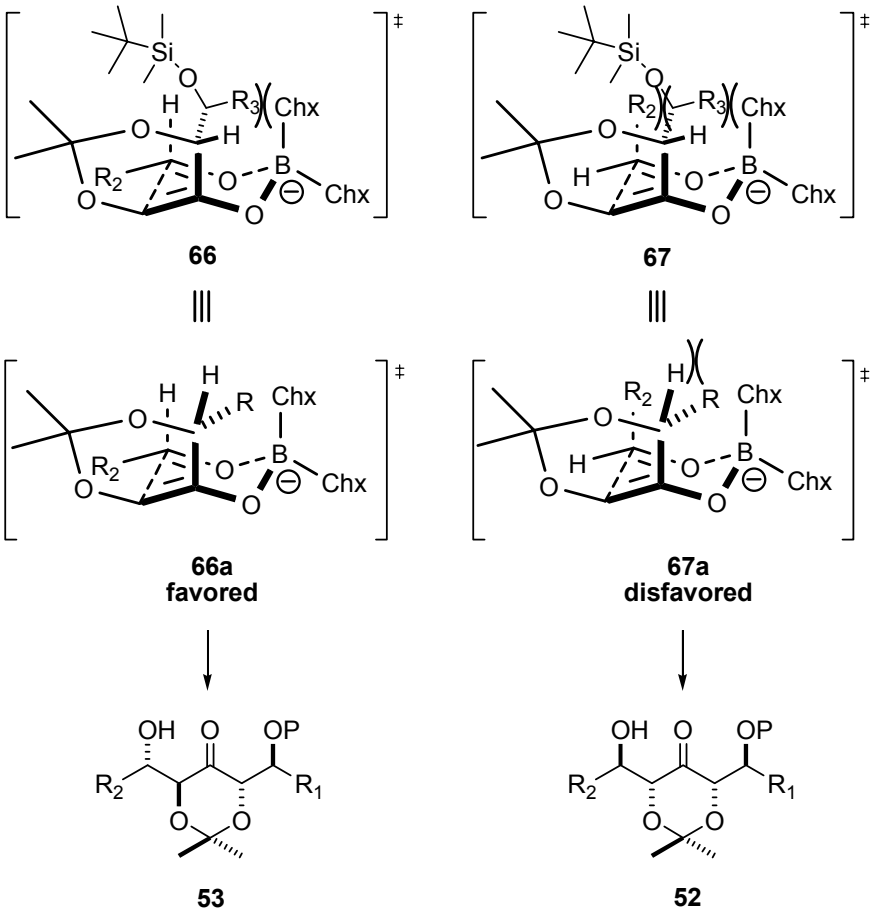
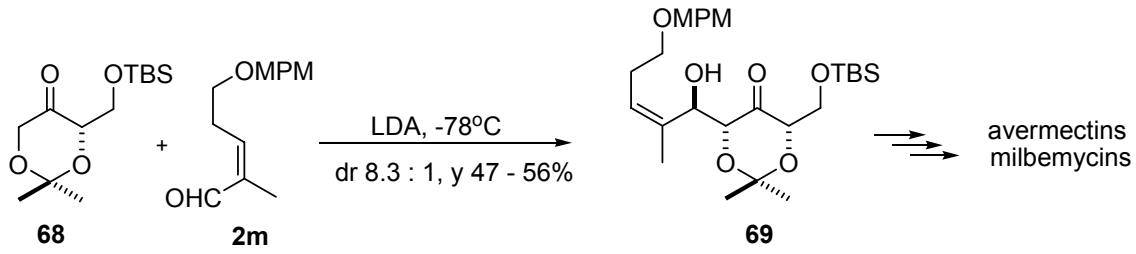



**Figure 2.14** Proposed transition state of dioxanone boron enolate addition to aldehydes

There are some literature precedents of the equatorial attack in a second aldol reaction mediated by lithium base. One relevant example was reported by Hirama in 1988. Synthesis of the subunit of the avermectins and the milbemycins was developed and the key in this approach was an aldol reaction (Scheme 2.26).[62] Even though that was clearly interesting observation no direct explanation was proposed to support experimental results.




**Scheme 2.26**

Stereochemical outcome in reactions of enolates depends predominantly on the structural properties of substrates and it might be not very sensitive to the nature of the electrophile. It is well known that the solvent and the counterion might play important roles in diastereofacial selectivity. To fully understand the transition state in lithium enolate reactions of dioxanone one has to consider aggregation of enolates.[69-71] It is well established that ketone and ester lithium enolates exist as aggregates in ethereal solvents (Figure 2.15).

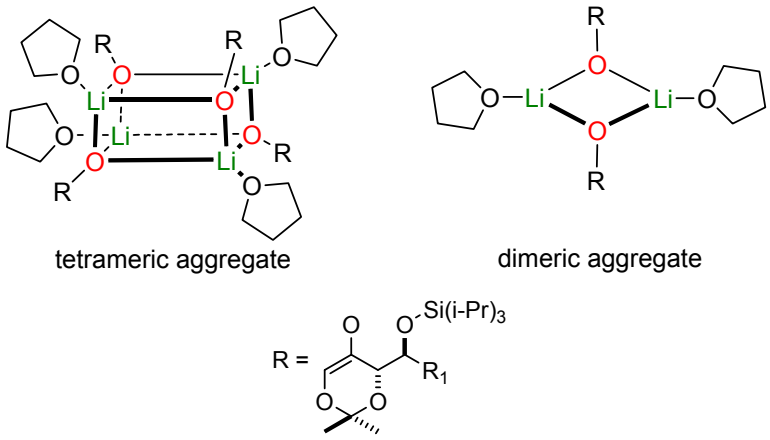



**Figure 2.15** Lithium enolate structures: dimeric or tetrameric aggregates in ethereal solvents

In addition to the aggregated nature of lithium enolates, LDA can complex to more then one Lewis base centers. That would be in agreement with the experimental data since more then 1 equivalent of LDA was required for enolization (see section 2.6.1 for details).

It is possible that the complexation of the lithium base lead to the formation of the transition state presented in Figure 2.16. Please note that only the chair – like transition state was taken into account and no aggregates were included in the drawing for simplification.

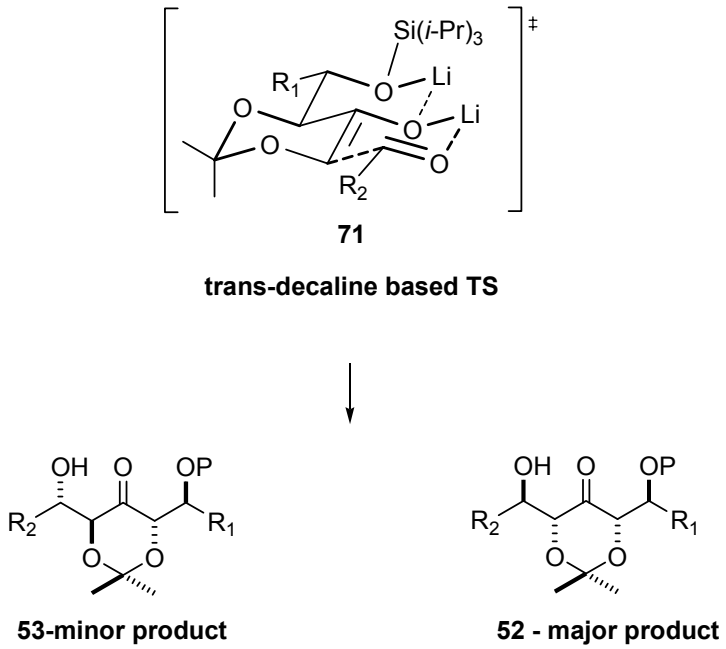



**Figure 2.16** Proposed transition state in the aldol reaction of dioxanone Li-enolate

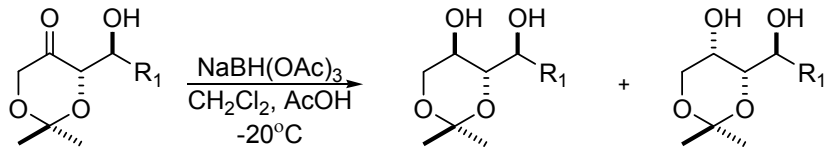
Presumably formation of diastereoisomer *trans* **53** requires the *cis*-decaline based transition state, which is known to be less favoured then *trans*-decalines.[72]

On the other hand, thermodynamic conditions (most probably, present in the case of (*S*)-proline catalyzed aldol reaction) should lead to the most stable product. It should be noted, that when a lithium base[21] or organocatalysis were employed for the first aldol reaction, the same aldol adducts, resulting from the equatorial attack, were obtained. Possibly, the dioxanone unit exists predominantly in a twist boat conformation and the substituent is placed in a pseudo-equatorial position, which might be favoured under both kinetic and thermodynamic conditions. At this point, however, I could not provide any reasonable argument to support the stereochemical outcome from these processes. Clearly, more research is needed to gain further understanding of the details of these operationally simple, nevertheless mechanistically complex reactions.

## 2.9 Reduction of bisaldols to the corresponding alcohols

According to the retrosynthetic plan (Figure 2.1), for carbohydrates one of the steps involved reduction of the carbonyl group to the corresponding alcohol. This section is not intended to be comprehensive in terms of exploring the versatility of all reducing reagents citied in the literature. Nonetheless, the data presented in the context of surveying this class of reactions should provide the reader with a reasonable overview of issues involved in reduction of bis aldol products. I will only briefly focus on that problem as the similar transformations on simple aldol products were studied already by others.[29, 73, 74]

Early in my studies I got interested in reduction of simple aldol adducts with sodium triacetoxyborohydride in the presence of acetic acid.[75] Starting materials having a masked aldehyde group (dithiane acetal or dimethoxy acetal) were investigated, since selective reduction could provide a quick access to D-ribose. As the result, protected D-riboses **72a** and **72b** were obtained in high diastereomeric ratio (de 96 – 98 %) and good yields (75 – 96 %). Summary of results are presented in Scheme 2.27. Worth mentioning is the *syn* selectivity (and not *anti*) that was rather unexpected from this protocol. This result (eventually proved by X-ray crystallography)[24] was in agreement with similar reports by both Barbas,[73] and Enders.[31, 74]



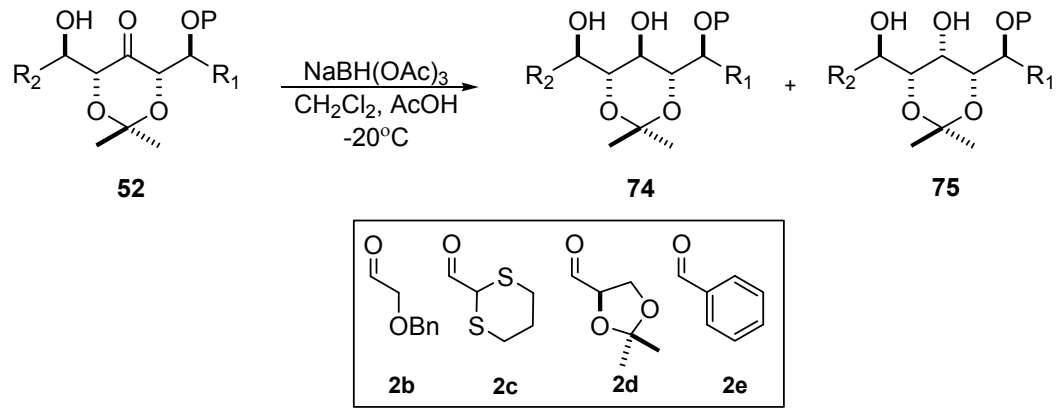

**7**
**7a:** $R_1$: $CH(OMe)_2$
**7b:** $R_1$: $CH(SCH_2)_2CH_2$

**72**
de 96%, y 75%
de 98%, y 96%

**73**

**Scheme 2.27**

Having completed selective reduction I applied this protocol to bis aldols. Results are summarized in Scheme 2.28 and Table 2.18.




**Scheme 2.28**

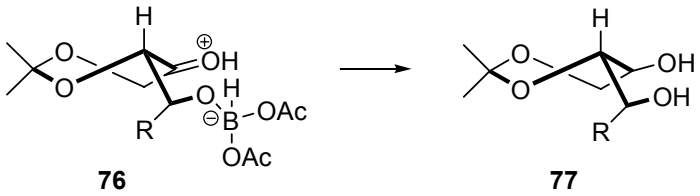
**Table 2.18** Reduction of **52** to the corresponding alcohol

| Entry | P | $R_1$ | $R_2$ CHO | 74 : 75 | Yield[a] |
|---|---|---|---|---|---|
| 1 | TIPS | *i*-Pr | **2c** | 16 : 1 | 94 |
| 2[b] | TIPS | *i*-Pr | **2e** | 8 : 1 | 65 |
| 3 | TIPS | $CH(OMe)_2$ | **2b** | 19 : 1 | 99 |
| 4[c] | TIPS | $CH(OMe)_2$ | **2c** | 3 : 1 | 62 |
| 5 | TBS | $CH(OMe)_2$ | **2c** | 19 : 1 | 85 |
| 6[c] | TBS | $CH(OMe)_2$ | **2c** | 3 : 1 | 67 |
| 7 | TBS | $CH(OMe)_2$ | **2e** | 30 : 1 | 83 |
| 8[c] | TBS | $CH(OMe)_2$ | **2e** | 2.2 : 1 | 80 |
| 9 | TBS | $CH(OMe)_2$ | **2d** | 21 : 1 | 93 |

[a] combined yield of isolated isomers, [b] $NaCNBH_3$ used as reducing reagent, [c]$NaBH_4$ used as reducing reagent

Typically the reduction with sodium triacetoxyborohydride proceeded with very good syn diastereoselectivity (16: 1 to 30 : 1, entries 1, 3, 5, 7, 9) and good to excellent yield (83 – 99 %). The utility of other hydrides, mild reducing reagents, was briefly investigated, however lower selectivities and yields were observed. Sodium borohydride gave the mixture of 1,3-diols in a 2.2 : 1 ratio and 80 % yield (entry 8), and sodium cyanoborohydride, know as a good reagent for reductive amination,[76] gave the mixture of isomeric alcohols in a 8 : 1 *cis* to *trans* and 65 % yield (entry 2). The lower yield in this case might be due to the hydrogenolysis reactions and opening of the acetal moiety.

The stereochemical outcome from the reduction could be explained by considering an intermolecular hydride transfer from boron reagent to carbonyl group. The method was developed by Evans,[75] who proposed the ligand exchange involving the boron reagent. It was established that α-alkylated starting materials led to *anti* diols; on the other hand reduction of α-O-benzylated compounds gave predominantly *syn* diols. If we considered reactive carbonyl moieties (like dioxanones) the reduction might proceed through an open transition state. Enders extrapolated Evans' theory to dioxanone chemistry and proposed that the dioxanone unit might exist predominantly in a twist boat conformation where the side-chain is placed in a pseudo-equatorial position. The hydride attacks the C=O group preferentially from the *si*-face to produce the *syn*-1,3-diol (Figure 2.17).[38]

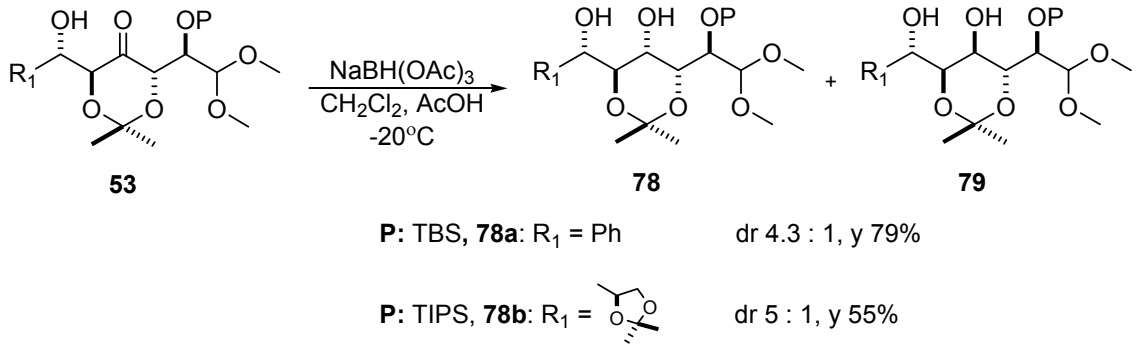



**76** **77**

**Figure 2.17** Proposed transition state for *syn* selective reduction by Enders[38]

Reduction of the *anti–trans–anti* aldols was also briefly studied. Results shown in Scheme 2.29 indicated that selectivities in that case were lower in comparison to the values obtained in the *syn* selective reduction of *anti–cis–anti* aldols. Reduction of **53**

with sodium triacetoxyborohydride proceeded in 55 - 79 % yield and 4.3 : 1 to 5.1 : 1 *syn* to *anti* ratio depending on the substrate at the α' position.




**Scheme 2.29**

This poor "stereochemical bias" might be explained based on a simple model outlined in Figure 2.18. Please note that only chair conformation is taken into consideration; the twist–boat conformation is not described, however one can apply similar rationalization as is presented for the chair conformation.

Structure **80** shows the major conformer for *anti-cis-anti* aldol, having both substituents in equatorial positions. Reduction of these systems usually proceeded in highly selective fashion (see Scheme 2.28 and Table 2.18 for details). On the other hand *anti-trans-anti* product, due to the *trans* relationship of α and α' chains, has to have one substituent in equatorial and second in axial position. Due to the rapid interconversion of such systems two chair conformations are possible **81a** and **81b**. As the result lower selectivity might be observed when *trans* aldols (in respect to the chains at α and α' of carbonyl group) are subjected for reduction.

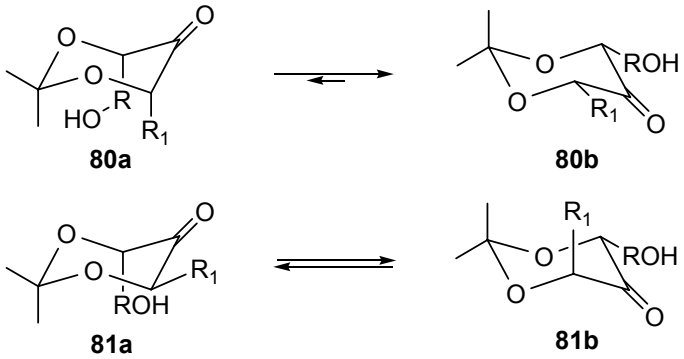



**Figure 2.18** Differences in conformation which might be responsible for selectivity in reduction with sodium triacetoxyborohydride of aldols.

This rationalization might explain the difference in the diastereoisomer ratio, which was low (approximately 4 or 5 to 1 *syn* to *anti* diol, Scheme 2.29) in comparison to the results obtained for *anti–cis–anti* aldols. As shown in Figure 2.18, in the major conformer of the α,α' *cis* substituted dioxanone **80b**, the hydroxyl group can be easily located in axial position due to the lack of steric restriction. On the other hand, the presence of one of the bulky substituents at the axial position in structures **81a** and **81b** disadvantages formation of *syn* diols in highly selective fashion.

## 2.10 Synthetic applications

My research objectives included developing the methodology for synthesizing sugars based on the dioxanone building block. In order to develop such approach, some requirements had to be fulfilled.

Firstly, the optimization of the reaction conditions for the first aldol reaction had to be undertaken. As described above, this was accomplished by organocatalysis - a simple method that allowed quick access to optically pure products.

Secondly, development of the suitable reaction conditions for the second aldol was necessary. A wide range of approaches was investigated including the area of metal enolate chemistry. Lithium enolate strategy was found to be the most suitable, but the excellent potential of boron enolate chemistry was noted.

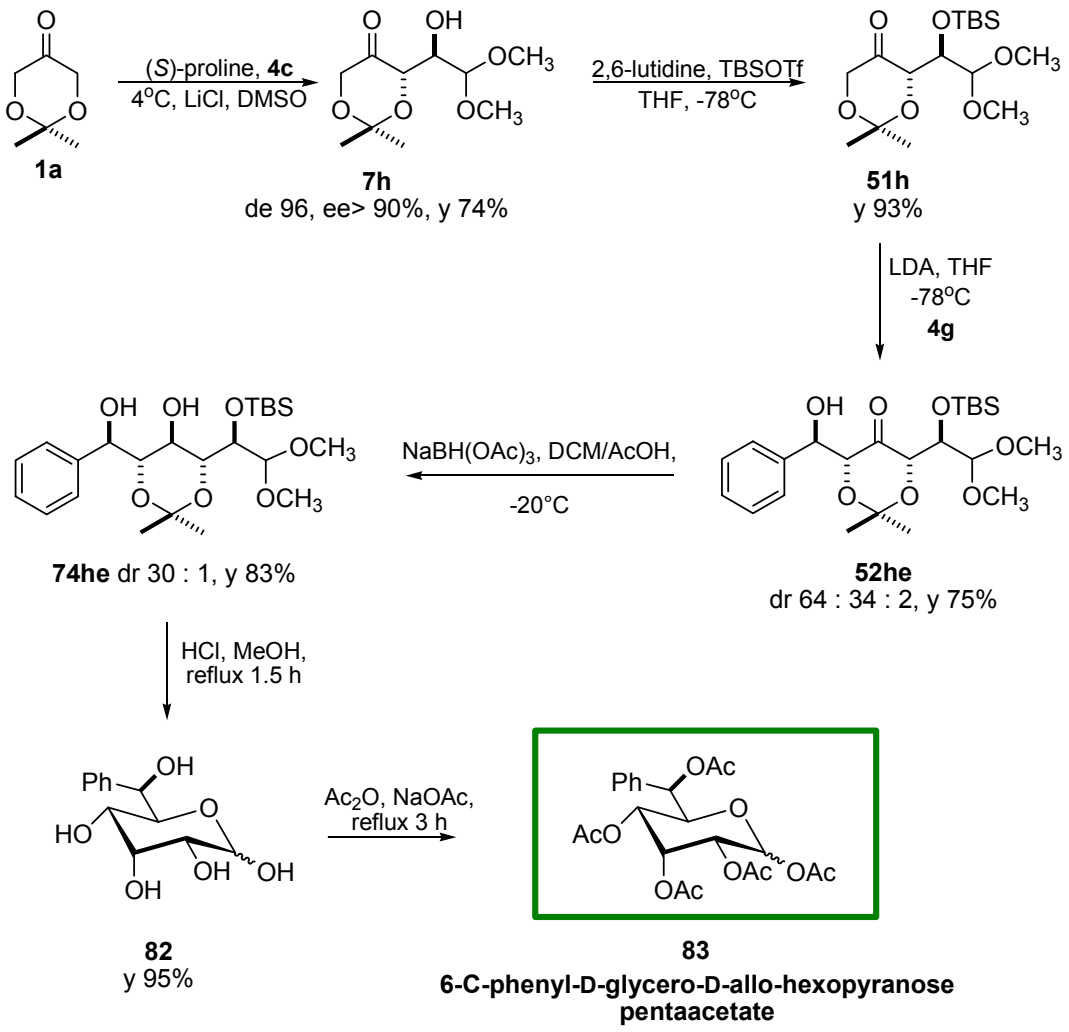
Stereochemical issues were solved by a series of experiments, comparison of the spectroscopic data with the known compound; stereochemistry of which was correlated with a commercially available sample. Moreover, X-ray crystallography as well as extensive NMR studies to support the relative and absolute configuration of products gave useful information.

The conditions for selective reduction of the α-α'-substituted ketones were successfully developed and the corresponding diols were obtained in high diastereoselectivity and yield.

The stage was now set for the last part of my project, involving the application of the dioxanone based strategy to synthesis of carbohydrates. Below, I highlight selected conversions of the bisaldol products to the corresponding carbohydrates.

### 2.10.1 Synthesis of 6-C-phenyl-D-glycero-D-allo-hexose

Derivatives of simple aldohexoses having an alkyl or aryl group connected to C-6 are important biologically active compounds.[77] The bisaldol strategy offers a quick access to these modified carbohydrates. Variety of alkyl substituents (cyclic, acyclic) might be easily introduced at the C-6 position, as it is only the issue of the proper choice of the aldehyde in the second aldol reaction.




**Scheme 2.30**

I decided to synthesize a 6-phenyl derivative of allose (**82**) shown in Scheme 2.30. Starting from 2,2-disubstituted dioxanone (**1a**) the β-hydroxyketone (**7h**) was obtained via the (*S*)-proline catalyzed aldol reaction in high selectivity. The yield of 74 % seemed to be relatively low, especially if we took into account that this was just a first step in the synthesis. However it is worth mentioning that the aldehyde used for this protocol existed as an aqueous solution, so we could assume that the reaction occurred in water. Protection of **7h** under standard conditions led to the formation of the silylated aldol **51h** in 93 % yield. Lithium mediated aldol reaction, using the protocol described in previous chapter provided a mixture of the aldol adducts.

Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at 5.12 ppm (d, *J*=4.6 Hz), 4.89 ppm (d, *J*=8.4 Hz), 4.78 ppm (d, *J*=8.4 Hz) and was found to be 2 : 64 : 34.

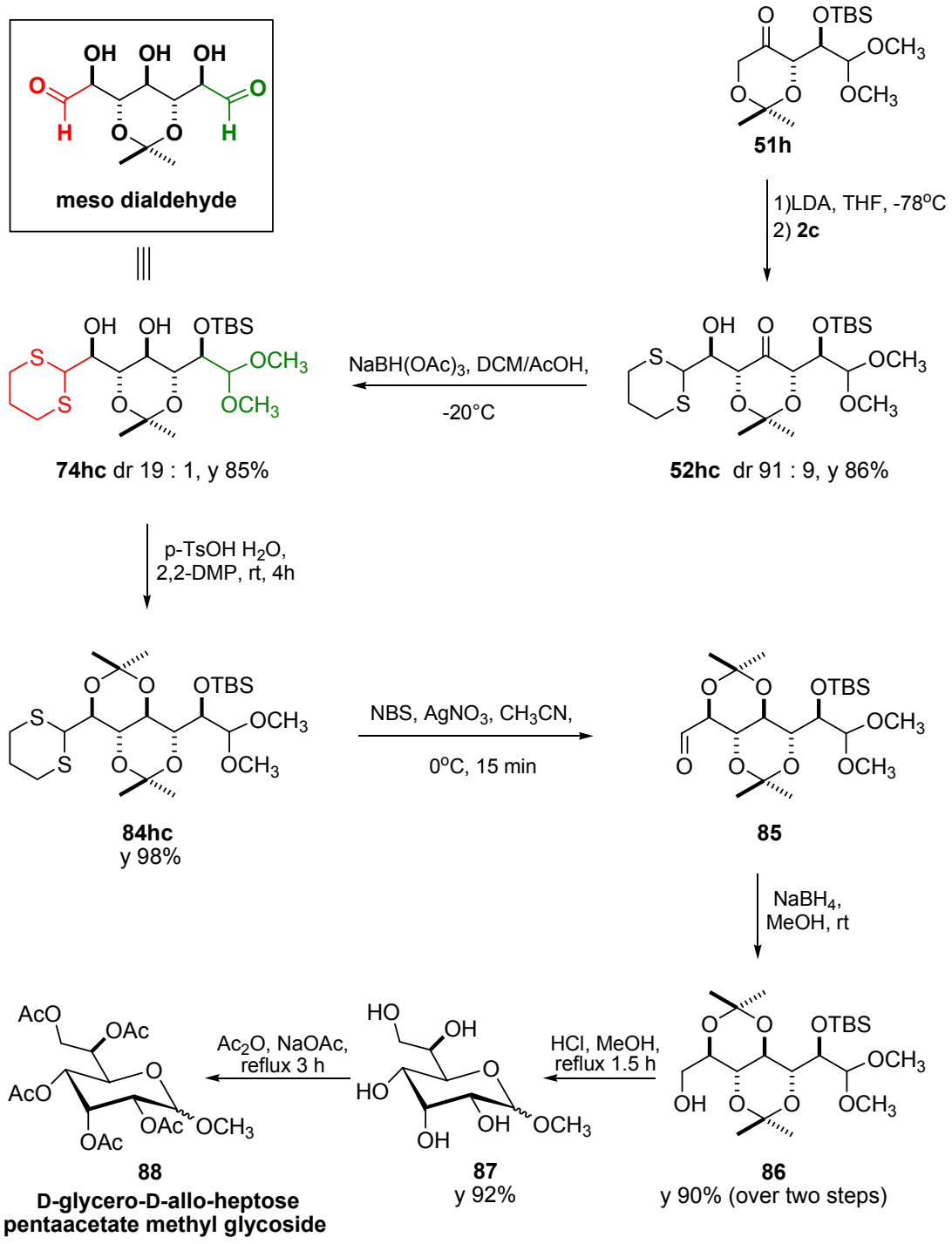
I applied previously described approaches to assign the stereochemistry of the products formed in this process (see section 2.7 for details.) The *anti-cis-anti* compound **52he** was obtained as a single isomer in 50 % yield. Reduction with sodium triacetoxyborohydride[75] gave the corresponding diol in 83 % yield and 30 : 1 (*syn* to *anti*) diastereoisomeric ratio. Deprotection of the three hydroxyl groups and the formyl group proceeded smoothly in "one pot" upon treatment with HCl affording the carbohydrate **82**, that was characterized as the acetate derivative, 6-C-phenyl-D-glycero-D-allo-hexopyranose pentaacetate **83** (overall yield 27 % in 6 steps).

### 2.10.2 Synthesis of D-glycero-D-allo-heptose

Synthesis of D-glycero-D-allo-heptopyranose (**88**) is shown in Scheme 2.31. Protected aldol **51h (**obtained from dioxanone in 2 steps) subjected to lithium base mediated aldol reaction provided a mixture of two compounds in 86 % yield. The diastereoisomer ratio of the reaction was determined by $^1$ H NMR on the crude product by integration of the characteristic peaks at 3.43 ppm and 3.35 ppm and was found to be 9 : 91 *anti-trans-anti* to *anti-cis-anti* aldols. The major component of the mixture **52hc,** isolated in 82 % yield, was selectively reduced to the corresponding diol in 95 : 5 *syn* to *anti* ratio.

It should be noted that this interesting compound is synthetically equivalent to the orthogonally protected *meso* dialdehyde. The $C_S$ symmetry of the latter compound should, in principle, allow a stereodivergent synthesis of either enantiomer of the final aldoheptose (depending on which formyl group is ultimately reduced). To date I have carried out this sequence only one way as follows: diol **74hc,** after being efficiently protected with 2,2-dimethoxypropane in the presence of *p*-TsOH, was subjected to dithiane hydrolysis using protocol developed by Corey.[78] The resulting aldehyde **85** was reduced to the alcohol **86** in 90 % yield over 2 steps. The product **86** was deprotected

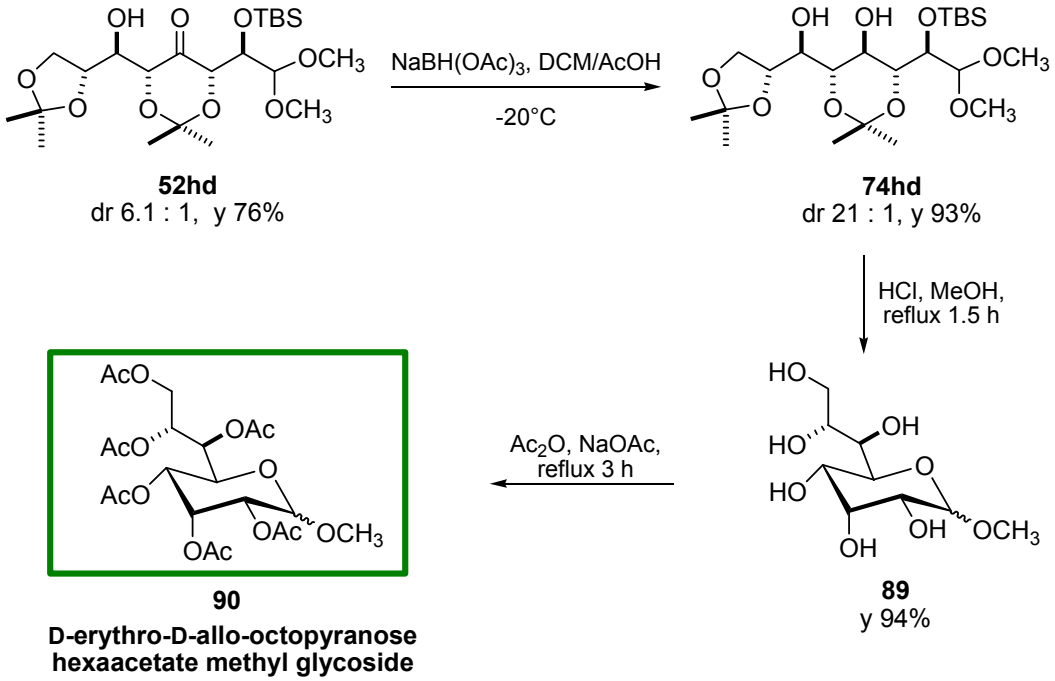
under acidic conditions to afford the heptose **87** in 39 % over 8 steps. The desired heptose was characterized as the pentaacetate methyl glycoside **88**.




**Scheme 2.31**

### 2.10.3 Synthesis of D-erythro-D-allo-octose

Similar approach was applied to the synthesis of aldooctose **90**. A straightforward approach (*vide supra*) allowed the formation of the bisaldol **52hd** in 57 % as a single isomer. Further transformations (reduction/deprotection) allowed for formation of the octopyranose **89** in 34 % yield over 5 steps. As previously, due to the difficulty with characterization, the final product was derivatized and characterized as a form of D-erythro-D-allo-octopyranose hexaacetate methyl glycoside **(90)**.

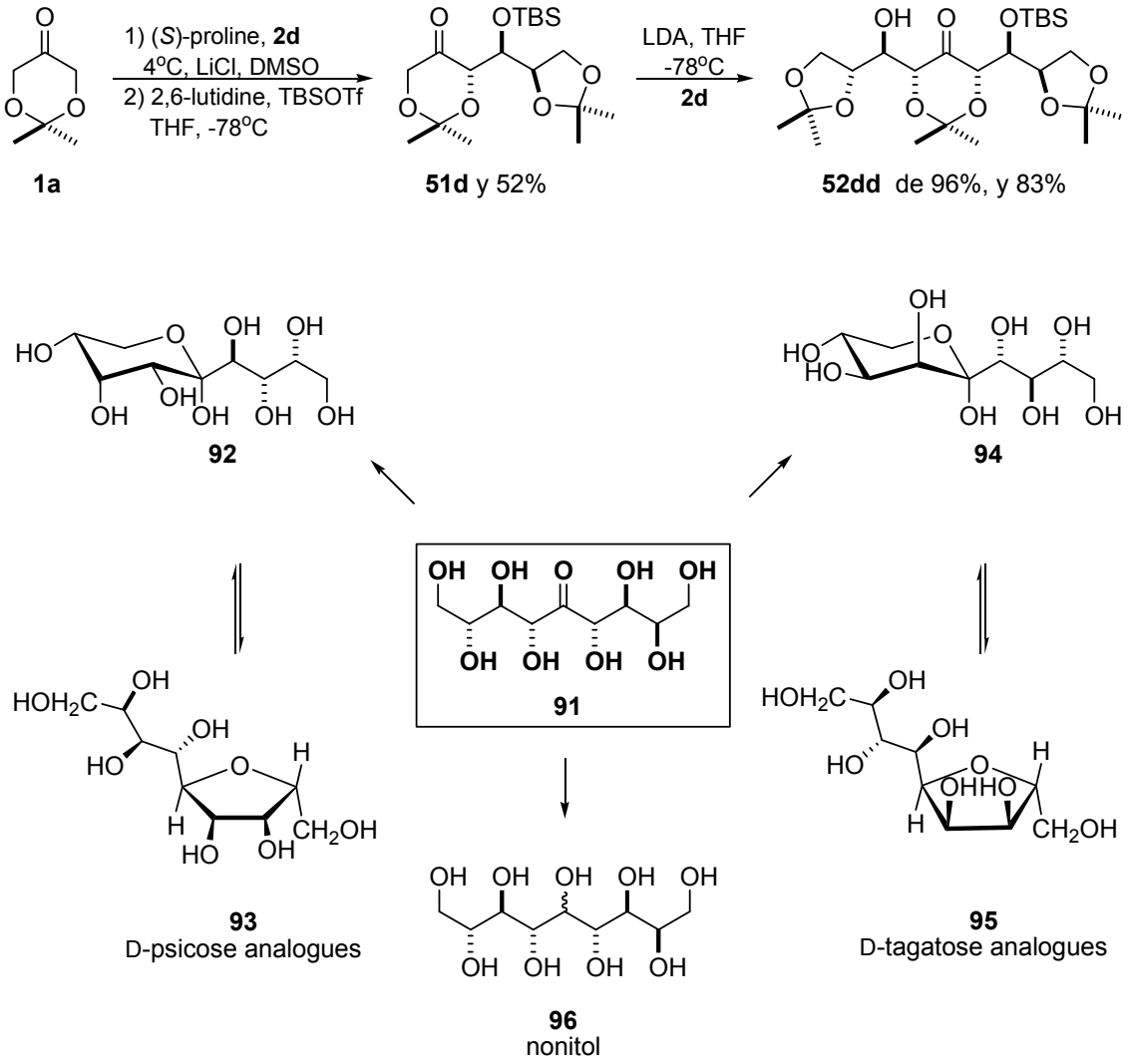



**Scheme 2.32**

### 2.10.4 Potential synthesis of nonoses and nonitols

Prospective uses of dioxanones to synthesis of D-psicose and D-tagatose analogs, as well as nonitols (poly hydroxylated nine-carbon fragments) are presented in the Scheme 2.33. This approach requires two consecutive aldol reactions of dioxanone **1a** with (*R*)-glyceraldehyde. The corresponding aldol product might be subjected to acetal deprotection to form, presumably, a mixture of pyranoses and furanoses of psicose and tagatose. Moreover, selective reduction of the carbonyl group of **52dd** or **91**

could give a quick access to the analogous nonitols **95**. This work was not carried out experimentally, due to the lack of time.

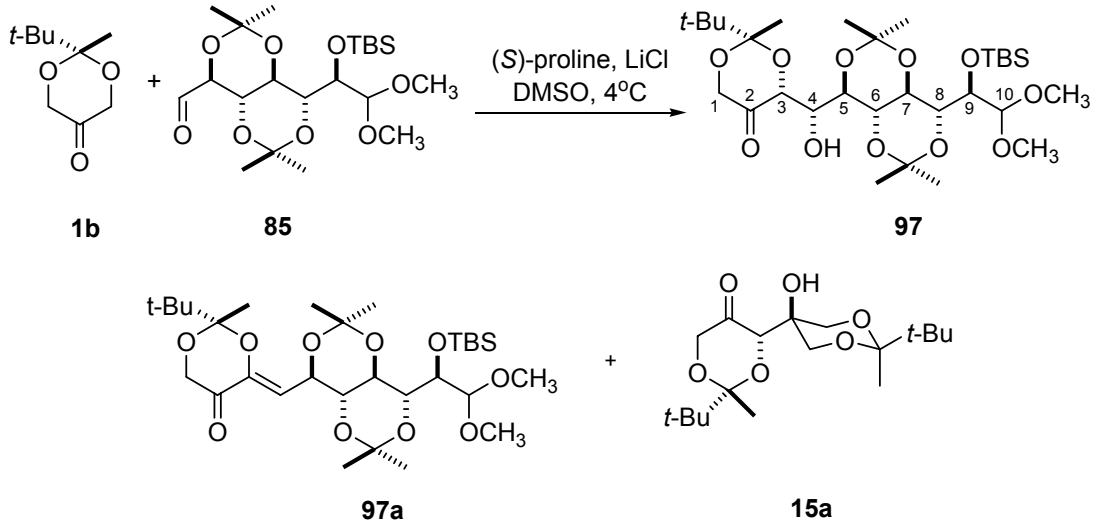



**Scheme 2.33**

### 2.10.5 A divergent synthesis of a decose precursor

As one of the ongoing projects in our laboratory I worked on the utility of the dioxanone based approach in a divergent synthesis of a decose (Scheme 2.34). As a part of this strategy I synthesized aldehyde **85** in 45 % yield in 6 steps starting from

dioxanone. Next, the direct aldol reaction was deliberately run with 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one **1b**, as it has been already proven to give better selectivity then the 2,2-dimethyl substituted ketone in proline-catalyzed aldol reaction.[24, 42] The conditions developed in our laboratories (with LiCl used as an additive), led to the formation of 3 products in a 1 : 5 : 9 ratio, having the characteristic peaks at 5.88 ppm, 4.73 ppm and 4.44 ppm ($^1$H NMR). Further analysis, possible only after purification, allowed the stereochemistry assignments of the compounds obtained in this process. One of them was the aldol condensation product (**97a**) isolated in less than 1 % yield, than dioxanone dimer (**15a**) isolated in 30 % yield and aldol product **97** formed in 25 % yield.




**Scheme 2.34**

Careful inspection of the crude NMR spectra as well as analysis of NMR data of **97** suggested that the only aldol product formed in this reaction was showing an unexpected *syn* relative configuration around the newly formed bond. The coupling constant of CH-3 and CH-4 was 3.2 Hz, that according to Heathcock,[63] indicated *syn* relative configuration. Fragment of the $^1$H NMR spectra showing all the characteristic signals of **97** is depicted in Figure 2.19.

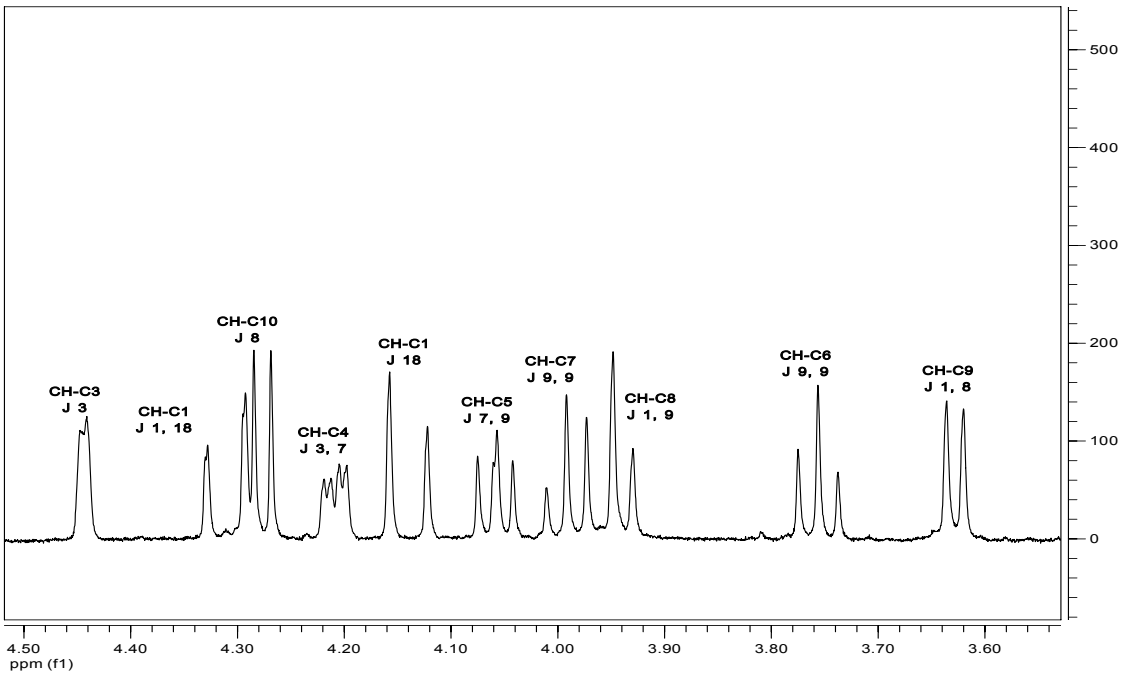



**Figure 2.19** $^{1}$H NMR spectra of compound **97** (only CH area shown)

Obviously, further studies are necessary for fully proving the stereochemistry, however at that point it seems that in this system the aldol reaction is *syn* selective.

Potential utility of the compound **97** in a divergent synthesis that might lead to a ketodecose **99** or an aldodecose **98** is depicted in the Figure 2.20.

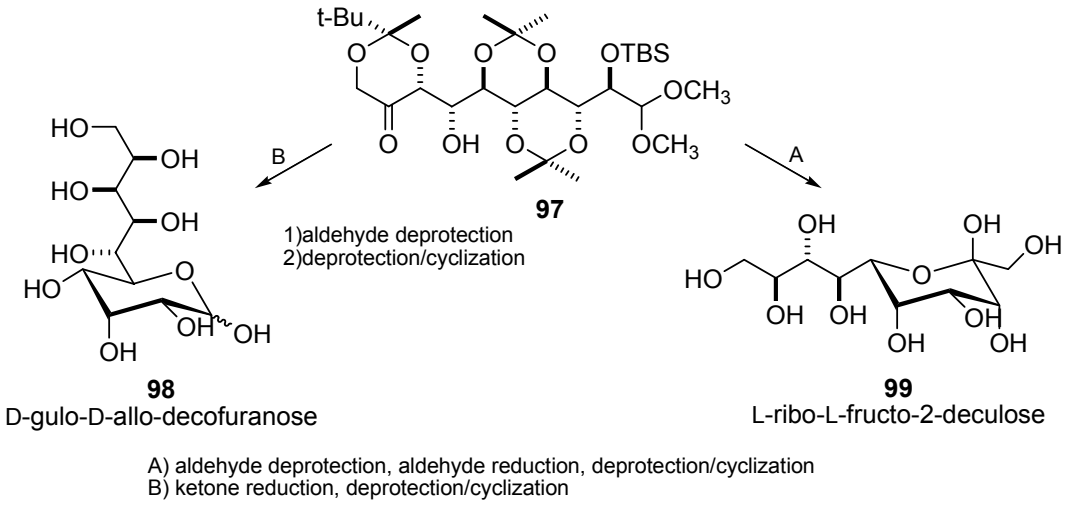


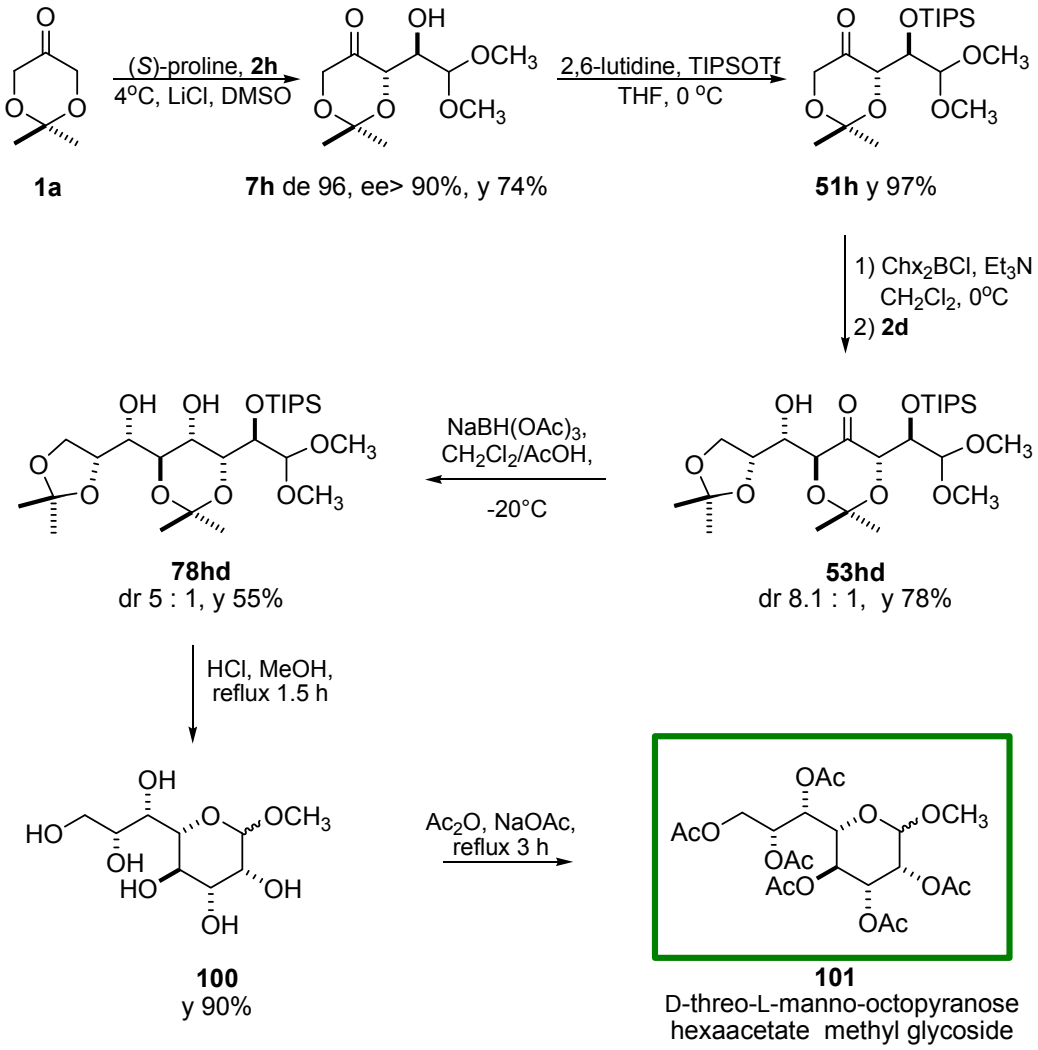

**Figure 2.20** Potential utility of the compound **97** in a divergent synthesis

### 2.10.6 Synthesis of D-threo-L-manno-octose

As one of the examples of carbohydrate synthesis, in which boron enolate was used as the tool for introducing the carbon chain at α' position, I tackled D-threo-L-manno-octopyranose, as L-sugars were already proven to be the compounds of importance (many bioactive metabolites possess unusual carbohydrates required for molecular recognition) and they have interesting properties.[79, 80] The synthesis of this unnatural sugar is presented in Scheme 2.35.

Proline catalyzed aldol reaction of **1a** and protection with TIPSOTf in the presence of a tertiary amine provided the silylated α - substituted dioxanone in 72 % yield over 2 steps. Boron mediated aldol reaction under previously described conditions,[27] provided a mixture of aldols in 8.1 : 1 ATA to ACA ratio. The product of interest **65hd** was isolated in 70 % yield as a single isomer. Reduction with sodium triacetoxyborohydride was found to be unselective and it furnished the mixture of *syn* and *anti* diols in a 5 : 1 ratio. Moreover, the yield of the reaction was low (55 %; 75 % based on recovered staring material). Those observations were consistent with the proposed model (see structure **81a** and **81b** in Figure 2.18) in which the presence of one of the substituents in the axial position next to the carbonyl group is responsible for steric hindrance and directing the hydroxyl group in reduction process.

The final step required deprotection of the acetal, the acetonide, TIPS and the formyl group which was achieved in one step and the glycoside **100** was formed in 25 % yield after 5 steps. As previously, the final product was characterized as the acetylated derivative **101**.


(S)-proline, 2h
4°C, LiCl, DMSO
2,6-lutidine, TIPSOTf
THF, 0 °C
1a
7h de 96, ee> 90%, y 74%
51h y 97%
1) Chx2BCl, Et3N
CH2Cl2, 0°C
2) 2d
NaBH(OAc)3,
CH2Cl2/AcOH,
-20°C
78hd
dr 5 : 1, y 55%
53hd
dr 8.1 : 1, y 78%
HCl, MeOH,
reflux 1.5 h
Ac2O, NaOAc,
reflux 3 h
100
y 90%
101
D-threo-L-manno-octopyranose
hexaacetate methyl glycoside

**Scheme 2.35**

## 2.11 Conclusions

The chemistry of dioxanones was successfully expanded. However, as previously reported, alkylation and acylation of these compounds *via* enolate chemistry remained the problem. On the other hand the aldol reaction can be easily conducted. The efforts concentrated at introducing a one-, two-, three-, four- and five– carbon chains to the dioxanone system were largely successful by employing organocatalysis, lithium or boron enolate chemistry. There was no generally superior method for accomplishing all those transformations; in each case there were some limitations:

**1)** Organocatalysis proved an excellent tool for the "first aldol" reaction; however some donors and acceptors failed to react under proline catalyzed conditions. On the other hand, this method, including modified derivatives of proline, was absolutely useless for the "second aldol" reaction. Under standard reaction conditions proline did not facilitate installation of the subunits at the α' position. Control of the stereochemistry, as well as the direction in the ratio of the products formation might be achieved by addition of weak Lewis acids as co-catalysts as well as by changing the substituent at quaternary carbon of the dioxanone ring.

**2)** Boron enolate chemistry, previously well researched by our group and by others, was found to have the limitation of not working well with reagents containing the dithiane moiety. Under the necessary oxidative cleavage, sulfur underwent unspecified transformations and the corresponding mixture was difficult to separate. Nonetheless, aldehydes which lack the dithiane moieties in their structures were successfully used in the mono- and bis- aldolization reactions involving boron enolates of dioxanones, providing the corresponding aldol (or bisaldol) adducts in high selectivity and yield.

**3)** The lithium mediated aldol reaction proved the most general method for reactions leading to bis aldols, especially after some of the problems (dimerization, reduction) solved by our group previously were taken under consideration. Optimization of the amount of base, essential for the desired transformation, led to the development of the

set of conditions in which most of the electrophiles successfully reacted to furnish the aldol products. Despite the fact that lithium enolate chemistry proved to be general, it suffered from a relatively low selectivity. During the methodology studies some stereochemistry issues were solved. NMR Studies together with some chemical experimentation led to the conformation of the stereochemistry outcome from lithium mediated aldol reaction

As far as the synthesis of higher sugars is considered, a double aldol strategy was successfully realized for the first time. A few questions had to be answered:

**1)** Stereocontrol (enantio- and diastereoselectivity) in the first aldol reaction of the symmetrical dioxanone building block was accomplished by employing organocatalysis as the tool. High diastereoselectivity (*anti* versus *syn*) was achieved by using proline (note that some proline derivatives provide *syn* selectivity, which might be the advantage in building diverse compounds). Enantioselectivity in those transformations was enhanced by using weak Lewis acids as co-catalysts.

**2)** Stereochemistry in the second aldol reaction could be manipulated by choosing the proper metal for the second aldol reaction. Simple experimentation indicated that there was no "substituent dependency", involving the substitution on the dioxanone ring, on selectivity of the second aldol reaction.

**3)** Reduction of the carbonyl group in dioxanone aldols and bisaldols was done by using the Evans protocol. High diastereoselectivities and chemical yields were obtained, although relatively long reaction times were required.

**4)** Organocatalysis and enolate chemistry were successfully applied in synthesis of 6-substituted hexose, aldoheptose and aldooctose. The potential for synthesis of other, differently substituted hexoses (at C-6) as well as nonoses and polyols was demonstrated.

**5)** During the methodology studies some stereochemistry issues were solved. NMR Revision, together with chemical experimentation allowed a firm establishment of the stereochemistry outcome from lithium and boron mediated aldol reaction of dioxanones.

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# CHAPTER 3

# 3. Experimental section

## 3.1. General Methods:

All air-sensitive reactions were carried out under nitrogen. All solvents were distilled prior to use. Anhydrous solvents were distilled under atmosphere of nitrogen as follows: tetrahydrofuran (THF), diethyl ether ($Et_2O$) and benzene (PhH) from benzophenone sodium ketyl; dichloromethane ($CH_2Cl_2$) and toluene ($PhCH_3$) from calcium hydride ($CaH_2$), diisopropylamine (DIA), triethylamine (TEA), diisopropylethylamine (DIPEA) and pyridine were distilled from calcium hydride ($CaH_2$) under nitrogen and stored over 4 A molecular sieves. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were dried with ($CaH_2$) according to the known procedures.[1] All liquid aldehydes and acetic anhydride ($Ac_2O$) were distilled and stored under nitrogen, dimethoxyacetaldehyde was used as an aqueous solution (60 %). *n*-BuLi was periodically titrated using 2,5-dimethoxybenzyl alcohol as the indicator. LiCl was dried at 130 - 150 °C under vacuum overnight, and it was kept under nitrogen. It used as a solid. All other commercially available reagents were used as received without further purification, unless stated otherwise. Concentrated phosphate buffer, used to quench reactions, was prepared by dissolving $Na_2HPO_4$ (47 g) and $NaH_2PO_4$ (32 g) in $H_2O$ (0.50 L).

All experiments involving air- and/or moisture-sensitive compounds were conducted in flame dried round-bottom flasks (or vials) capped with rubber septa, and attached via a needle and connecting tubing to a nitrogen manifold. Low temperature baths were ice/water (0 °C), ice/acetone (-10 °C ), ice/NaCl/MeOH (-20 °C), $CO_2$(s)/isopropanol (-30 °C) and $CO_2$(s)/acetone (-78 °C). Reaction temperatures refer to the bath temperature.

Preparative TLC (PTLC) and TLC were carried out on glass plates (20 x 20 cm) precoated (0.25 mm) with silica gel 60 F254. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of:

1) Potassium permanganate (1.5 g) in water (0.20 L) containing $K_2CO_3$ (10 g) and NaOH (1.2 mL, 10 %), or the solution of

2) Phosphomolybdic acid hydrate (40 g), cerium(IV) sulfate (10 g) and concentrated sulfuric acid (50 g) in distilled water (1.0 L) followed by charring on a hot plate.

As the visualization of some of the oxygenated compounds was not possible by using solutions described above, other stains were considered:

3) *p*-Anisaldehyde (1.0 mL), concentrated sulfuric acid (9.5 mL), concentrated acetic acid (2.7 mL,) dissolved in EtOH (0.25 L)

4) Vanillin (1.5 g) dissolved in EtOH (0.10 L) containing concentrated sulfuric acid (1.0 mL).

The term "concentrated" refers to removal of solvents at a water aspirator pressure on a rotary evaporator.

Flash column chromatography (FCC) was performed according to Still[2] with Merck Silica Gel 60 (40 - 63 μm). Dry flash column chromatography (DFC) was performed according to Harwood.[3] All mixed solvent eluents are reported as v/v solutions.

**3.2. Spectral Data:**

Melting points and boiling points are uncorrected. Melting points were measured on a Gallencapm melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter (1 dm, 1 mL cell). All concentrations are quoted in grams per 100 mL.

IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported.

Unless otherwise noted, nuclear magnetic resonance (NMR) spectra were recorded on Bruker at 500 MHz for $^{1}H$ and 125 MHz for $^{13}C$ in the deuterated solvents stated. Signals due to the solvent ($^{13}C$ NMR) or residual protonated solvent ($^{1}H$ NMR) served as the internal standard: $CDCl_3$ (7.24 δH, 77.23 δC); $CD_3OD$ (3.31 δH, 49.15 δC); $C_6D_6$ (7.16 δH, 128.39 δC). The $^{1}H$ NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Multiplicity was indicated by one or more of the following: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), t (triplet), m (multiplet), br (broad). Couplings constants (*J*) were reported to the nearest 0.5 Hz. The $^{1}H$ NMR assignments were made based on chemical shifts and multiplicities. Where necessary, 2D gradient COSY, and homonuclear decoupling experiments were used to aid assignment of assigning $^{1}H$ NMR spectra. The $^{13}C$ NMR assignments were made on the basis of chemical shifts and were confirmed, where necessary, by two dimensional $^{1}H/^{13}C$ correlation experiments (HSQC and/or HMBC).[4]

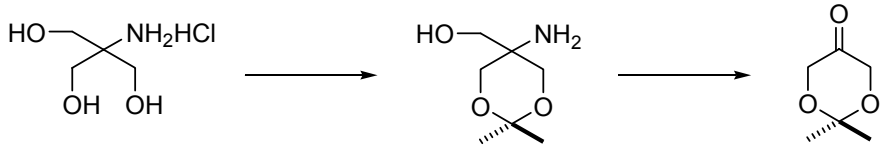
Aldol products were assigned to have relative configuration *syn* or *anti* based on the size of the vicinal C(O)-C<u>H</u>-C<u>H</u>-OH $^{1}H$ NMR coupling constant (*syn* $J$ = 2 – 6 Hz, *anti* $J$ = 7 – 10 Hz).[5]

Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained on a VG 70 E double focusing high resolution spectrometer; only partial data were reported. The techniques used were electron impact (EI) ionisation accomplished at 70 eV and chemical ionisation (CI) accomplished at 50 eV with ammonia as the reagent gas; only partial data are reported.

Each of experiments was repeated minimum three times. Occasionally the experiment did not work or proceeded with lower yield or/and selectivity for no obvious reason. Such experiments were rejected.

### 3.3. Synthesis of dioxanone starting materials

#### 2, 2-Dimethyl-1, 3-dioxan-5-one (1a)[6]




**102** **103** **1a**

This compound was prepared according to the known procedure. [6, 7]

Tris(hydroxymethyl) aminomethane hydrochloride (**102**) (35 g, 0.22 mol) and *p*-TsOH $H_2O$ (1.9 g, 10 mmol) were suspended in dry DMF (90 mL). 2,2-Dimethoxypropane (30 mL, 0.24 mol) was added and the mixture was stirred at room temperature for 40 h. Triethylamine (5.0 mL) was then added and the solvent was removed under reduced pressure. The residue was suspended in ethyl acetate (0.30 L) and triethylamine (50 mL) and stirred for 10 min. The precipitate was filtered off and the solvent was removed under reduced pressure to give (5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (**103**) (26 g, 0.16 mol, 73 %) as the white solid. The crude product was used in the subsequent step without purification.

Cold (0 - 5 °C) solution of sodium periodate (42 g, 0.20 mol, 1.3 eq) in $H_2O$ (0.35 L) was added over 70 min., at 0 °C, to the α-amino alcohol (**103**) (25 g, 0.15 mol) dissolved in $H_2O$ - MeOH (4 : 1; 0.25 L). The mixture was stirred at this temperature for 1.5 h. Next, the white suspension was filtered off and the solution was thoroughly extracted with $CH_2Cl_2$ (x 7). The combined organic layers were washed with a sodium bicarbonate solution (5 %; x 2), dried with magnesium sulphate and evaporated on a rotovap (temperature below 30 °C). Vacuum distillation of the crude product gave the pure 2, 2-dimethyl-1, 3-dioxan-5-one (**1a**) (19 g, 0.15 mol, 97 % yield) as a colorless liquid.

**$R_f$** 0.41 (hexanes : EtOAc 4 : 1)

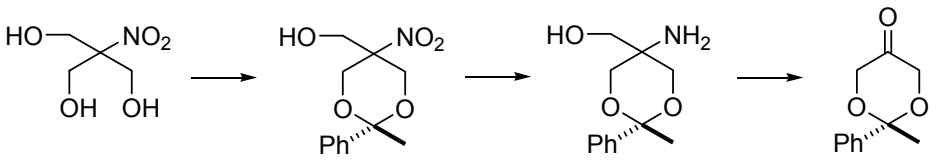
**b.p.** 54-55 °C/17 mm Hg, **lit**.[6] 67 °C/20 mm Hg

**IR** (KBr): 2855, 1743, 1456, 1374, 1225, 1091 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) δ: 4.13 (s, 4H), 1.43 (s, 6H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ*: 208.2, 100.3, 67.0, 23.7

**2-Methyl-2-phenyl-1,3-dioxan-5-one (1c)**




**104** **105** **106** **1c**

This compound was prepared according to the modified procedure[7]

Tris(hydroxymethyl) nitromethane (**104**) (7.6 g, 50 mmol) and *p*-TsOH $H_2O$ (95 mg, 0.50 mmol) were dissolved in dry benzene (150 mL). Acetophenone (6.0 mL, 6.1 g, 51 mmol) was added and the mixture was refluxed with removal of water (Soxhlet apparatus; 4A molecular sieves). After the reaction was completed (TLC and $^1$H NMR monitoring) the reaction mixture was cooled to room temperature and diluted with AcOEt (150 mL). Organic layer was washed with saturated solution of $NaHCO_3$ (x 3), dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield the crude product which was recrystalized with dichloromethane - hexane to give **105** in 53 % yield as the white solid (6.7 g, 26 mmol).

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ*: 7.42-7.34 (m, 5H), 4.62 (d, *J*=12.8 Hz, 2H), 3.82 (d, *J*=12.8 Hz, 2H), 3.66 (s, 2H), 1.50 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 138.2, 129.3, 128.7, 126.5, 101.9, 87.3, 64.0, 63.1, 31.1

A solution of (2-methyl-5-nitro-2-phenyl-1,3-dioxan-5-yl)methanol (**105**) (6.7 g, 26 mmol) was dissolved in methanol (100 mL). Raney nickel (ca 0.10 g) was added and the solution was stirred for 5 min, filtered, and a fresh portion of Raney nickel was added (ca 1.0 g). Reaction mixture was hydrogenated overnight (50 psi, room temperature). The catalyst was filtered off and the solvent was removed to provide the crude product **106** as a mixture of isomers in a ratio of 1 : 2 as a white solid (5.6 g, 25 mmol) in 96 % yield. No efforts were made to assign *cis*/*trans* configuration.

Major isomer:

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.41-7.36 (m, 5H), 3.60 (d, $J$=11.3 Hz, 2H), 3.52 (d, $J$=11.3 Hz, 2H), 3.10 (s, 2H), 1.55 (s, 3H)

Minor isomer:

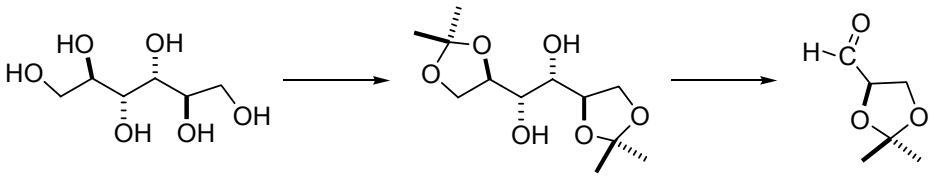
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.33-7.28 (m, 5H), 3.85 (s, 2H), 3.70 (d, $J$=11.5 Hz, 2H), 3.36 (d, $J$=11.5 Hz, 2H), 1.50 (s, 3H)

Cold (0-5 °C) solution of sodium periodate (1.3 g, 6.0 mmol, 1.5 eq) in $H_2O$ (10 mL) was added over 10 min. at 0 °C to the α-amino alcohol (**106**) (0.89 g, 4.0 mmol, 1.0 eq) dissolved in $H_2O$-MeOH (1 : 3; 10 mL). The mixture was stirred at this temperature for 3 h. Next, the white suspension was filtered off and the solution was thoroughly extracted with $CH_2Cl_2$ (x 4). The combined organic layers were washed with a sodium bicarbonate solution (5 %; x 2), dried with $MgSO_4$ and evaporated on a rotovap (temp < 30 °C). The crude product was purified by passing through silica (hexane : ethyl acetate 97 : 3) to give pure 2-methyl-2-phenyl-1,3-dioxan-5-one (**1c**) (0.68 g, 3.5 mmol, 89 %) as a colorless liquid.

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.51-7.33 (m, 5H), 4.25 (dd, $J_1$=1.2 Hz, $J_2$=17.3 Hz, 2H), 4.10 (dd, $J_1$=1.2 Hz, $J_2$=17.3 Hz, 2H), 1.65 (s, 3H)
**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 207.3, 141.0, 128.7, 128.6, 126.0, 101.2, 67.7, 27.2

### 3.4. Synthesis of aldehydes

**(*R*)-2,3-O-Isopropylideneglyceraldehyde (2d)[8]**




**107** **108** **2d**

This compound was prepared according to the known procedure.[8]

D-Mannitol (**107**) (5.1 g, 28 mmol) was dissolved in freshly distilled 1,2 dimethoxyethane (25 mL). Stannous chloride dihydrate (0.10 g, 0.44 mmol) and 2,2-dimethoxypropane (8.0 mL, 65 mmol) were added at room temperature. The stirred slurry was heated under reflux for about 2 h, until the mixture became clear (condenser was equipped in $CaCl_2$ drying tube). The reflux was maintained for another 30 min. than the solution was cooled down. Pyridine (20 μL) was added and the solvent was removed under reduced pressure (25 - 70 °C) to provide crude 1,2 : 5,6-diisopropylidene-D-mannitol (**108**) as a semi-solid.

Protected D-mannitol (5.2 g, 20 mmol) was dissolved in dry $CH_2Cl_2$ (50 mL) and the mixture was heated under reflux with vigorous stirring for 30 min. Celite (0.50 g) was added and the mixture was cooled down to r.t. followed by vacuum filtration. The filter cake was rinsed with $CH_2Cl_2$ (30 mL) and the flask was placed in a water bath. Saturated sodium bicarbonate (3.2 mL, 0.40 mL/g of diacetonide) was added with stirring and sodium periodate (6.6 g, 31 mmol) was added over 3 - 5 min. The resulting mixture was stirred (temperature was maintained bellow 35 °C) for 2 h. An anhydrous magnesium sulphate (3.5 g) was added and the solution was stirred for 20 min. The solvent was removed by simple distillation followed by vacuum distillation that

provided pure (***R***)-2,3-O-isopropylideneglyceraldehyde (**2d**) (2.8 g, 22 mmol, 40 %, lit. 34 - 45 %).

**2d** was stored in polymeric form and was cracked by vacuum distillation prior to use.

**$[\alpha]^{24}_D$** +43.1 (c 1.1, benzene), **lit.**[7] **$[\alpha]^{25}_D$** +54.3 (c 1.4, benzene)

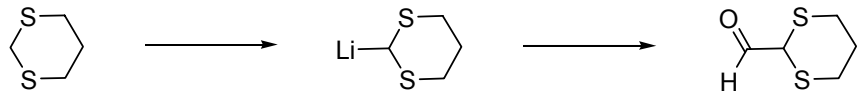
**b.p.** 56-59 °C/25 mm Hg, **lit.**[7] 67-70 °C/30 mm Hg

**$R_f$** 0.36 (hexane : ethyl acetate 1 :1)

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 9.70 (d, $J$=1.5 Hz, 1H), 4.37 (ddd, $J_1$=1.5 Hz, $J_2$=4.7 Hz, $J_3$=7.6 Hz, 1H), 4.15 (dd, $J_1$=7.6 Hz, $J_2$=8.8 Hz, 1H), 4.08 (dd, $J_1$=4.7 Hz, $J_2$=8.8 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 202.0, 111.5, 80.1, 65.8, 26.5, 25.4

**1,3-Dithiane-2-carbaldehyde (2c)**[9]




**109** **110** **2c**

This compound was prepared according to the known procedure.[9]

A solution containing 1,3-dithiane (**109**) **(**5.3 g, 44 mmol**)** in dry THF (100 mL) was cooled to -30 °C while stirred under nitrogen, and was then treated dropwise with *n*-BuLi (22 mL, 44 mmol, 2.0 M in hexane). After 1 h of additional stirring the solution was transferred by syringe to a flask containing previously cooled (-10 °C) DMF (14 ml, 1.3 g, 0.18 mol). The mixture was stirred for 2 h at -10 °C and then was stored overnight at 0 °C. The resulting suspension was poured into ice water (100 mL) and the mixture was extracted several times with hexane. The aqueous layer was neutralized with hydrochloric acid (1 N) until pH 4 and then extracted several times with ether. The ethereal extracts were dried with $MgSO_4$ and concentrated to give a viscous, cloudy oil that was distilled under reduced pressure to give the pure 1,3-dithiane-2-carbaldehyde

(**2c**) (5.5 g, 37 mmol) as a colorless liquid in 87 % yield. The product was stored at -20 °C to prevent dimerization, which occurred slowly at room temperature.

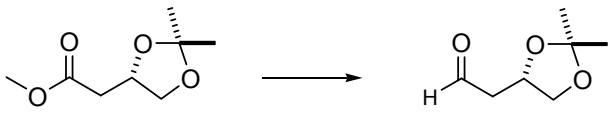
**$R_f$** 0.49 (hexanes : ethyl acetate 4 : 1)

**b.p.** 99-100 °C/2.3 mm Hg, **lit.**[9] 85 °C/0.5 mm Hg

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ*: 9.50 (s, 1H), 4.08 (s,1H), 3.05-2.99 (m, 2H), 2.57-2.53 (m, 2H), 2.10-1.95 (m, 2H), 1.54 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 188.4, 47.8, 25.6, 25.1

**(*S*)-2,2-Dimethyl-4-(2-oxoethyl)-1,3-dioxolane (2j)**[10]



**111** **2j**

Compound **111** was prepared using a modified literature procedure[10] in 3 steps in 65 % yield starting from (*S*)-malic acid).

**111** (0.64 g, 37 mmol) was dissolved in dry $CH_2Cl_2$ (160 mL) and the resulting solution was cooled down (acetone/dry ice bath). DIBAL-H (67 mL, 67 mmol, 1.0 M solution in hexanes, 1.8 eq) was added slowly over 4 h (syringe pump). The resulting solution was stirred at ambient temperature for 1 h, then quenched by addition of MeOH (100 mL) and warm up to rt. Diluted HCl (0.40 M, 85 mL) was added and phases were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 100 mL), the combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. Distillation under reduced pressure provided tilted compound as a colorless oil (5.3 g, 37 mmol, 100 %).

**b.p**. 74-77 $^{o}$C/17.5 mm Hg

**$[\alpha]^{22}_{D}$** + 13 (c 1.3, chloroform)

**$R_f$ 0.37** (hexane : ethyl acetate 1 : 1)

**$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$: 9.78 (dd, $J_1$=1.3 Hz, $J_2$=1.8 Hz, 1H, CH-C1), 4.50 (dddd, $J_1$=6.1 Hz, $J_2$=6.1 Hz, $J_3$=6.6 Hz, $J_4$=6.7 Hz, 1H, CH-C3), 4.16 (dd, $J_1$=6.1 Hz, $J_2$=8.3 Hz, 1H, CH-C4), 3.56 (dd, $J_1$=6.7 Hz, $J_2$=8.3 Hz, 1H, CH-C4), 2.81 (ddd, $J_1$=1.8 Hz, $J_2$=6.6 Hz, $J_3$=17.2 Hz 1H, CH-C2), 2.62 (ddd, $J_1$=1.3 Hz, $J_2$=6.1 Hz, $J_3$=17.2 Hz 1H, CH-C2), 1.39 (s, 3H), 1.33 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 200.2, 109.5, 70.9, 69.3, 27.0, 25.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 162 ($[M+18]^+$, 100), 145 ($[M+1]^+$, 77), 129 (35), 101 (10), 87 (12), 73 (7), 58 (10)

**HRMS** *m/z* calcd for $C_7H_{12}O_3$ 145.0865 (M+H), found 145.0861 (EI)

**3.5. Synthetic studies on the organocatalytic dioxanone aldol reaction ("the first aldol"). General procedures for (*S*)-proline catalyzed aldol reaction.**

Procedure P1. (*S*)-Proline catalyzed aldol reaction without additives

A dioxanone (0.50 mmol) and an aldehyde (0.50 mmol) were added to a flame-dried vial charged with (*S*)-proline (0.15 mmol). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and stored in a refrigerator at 4 °C for 1–7 d (TLC controlled reaction). The reaction was then quenched with sat. $NH_4Cl$ solution (5 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried with $MgSO_4$, concentrated and purified by flash column chromatography using silica gel (hexane : ethyl acetate 3 % - 60 %).

Procedure P2. (*S*)-Proline catalyzed aldol reaction with LiCl as the additive

A dioxanone (0.50 mmol) and an aldehyde (0.50 mmol) were added to a flame-dried vial charged with (*S*)-proline (0.15 mmol) and LiCl (0.15–0.50 mmol). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and stored in a refrigerator at 4 °C for 1 – 7 d. The reaction was then quenched with sat. $NH_4Cl$ solution (5 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried with $MgSO_4$, concentrated and purified by FCC using silica gel (hexane : ethyl acetate 3 % - 60 %).

Procedure P3. (*S*)-Proline catalyzed aldol reaction with pyridinium *para*-toluenosulfonate as the additive

A dioxanone (0.50 mmol) and an aldehyde (0.50 mmol) were added to a flame-dried vial charged with (*S*)-proline (0.15 mmol) and PPTS (0.15–0.50 mmol). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and stored in a refrigerator at 4 °C for 1–7 d. The reaction was then quenched with sat. $NH_4Cl$ solution (5 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed

with brine, dried with $MgSO_4$, concentrated and purified by FCC using silica gel (hexane : ethyl acetate 3 % - 60 %).

Procedure P4. (*S*)-Proline catalyzed aldol reaction at room temperature

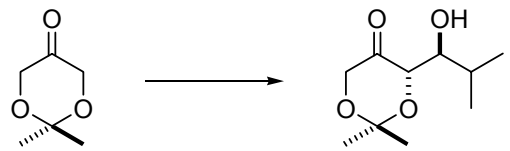
A dioxanone (0.50 mmol) and an aldehyde (0.50 mmol) were added to a flame-dried vial charged with (*S*)-proline (0.15 mmol). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and stirred at rt for 1–7d (TLC controlled reaction). The reaction was then quenched with sat. $NH_4Cl$ solution (5 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried with $MgSO_4$, concentrated and purified by flash column chromatography using silica gel (hexane : ethyl acetate 3 % - 60 %).

Procedure P5. (*S*)-Proline catalyzed aldol reaction under sonication conditions

A dioxanone (0.50 mmol) and an aldehyde (0.50 mmol) were added to a flame-dried vial charged with (*S*)-proline (0.15 mmol). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and ultrasonicated for 30 min. The reaction was then quenched with sat. $NH_4Cl$ solution (5 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried with $MgSO_4$, concentrated and purified by flash column chromatography using silica gel (hexane : ethyl acetate 3 %-60 %).

The diastereoisomer ratio was measured by $^1H$ NMR or $^{13}C$ NMR on a crude reaction mixture. The enantiomer ratio was measured by $^1H$ NMR on a pure product with shift reagent (NMR experiment was done in $CDCl_3$ or in $C_6D_6$ in the presence of $Eu(tfc)_3$ or (*S*)-(+)-TFAE). It was established that passing the crude mixture through a short column charged with silica did not alter the enantiomer ratio (even after repeated chromatography).

**4-(*S*)-4-[(*S*)-1-hydroxy-2-methylpropyl]-2,2-dimethyl-1,3-dioxan-5-one (7f)[11]**




**1a** **7f**

Procedure P1 afforded crude product as a yellowish oil. The ratio of diasteroisomers was measured by $^1$H NMR and was found to be 1 : 21. The crude product was purified by FCC (hexane : ethyl acetate 95 : 5) to provide the *anti* isomer in 65 % yield as a colorless oil. Enantioselectivity was measured by $^1$H NMR in $CDCl_3$ with (*S*)-(+)-TFAE as the shift reagent.

**$[\alpha]^{25}_D$** -169 (c 1.0, chloroform) (86 % ee)

Procedure P2 afforded crude product as a yellowish oil. The ratio of diasteroisomers was measured by $^1$H NMR and was found to be 1 : 61 The crude product was purified by FCC (hexane : ethyl acetate 95 : 5) to provide the *anti* isomer in 66 % yield as a colorless oil. Enantioselectivity was measured by $^1$H NMR in $CDCl_3$ with (*S*)-(+)-TFAE as the shift reagent.

**$[\alpha]^{25}_D$** -180 (c 1.4, chloroform) (92 % ee)

Procedure P3 afforded crude product as a yellowish oil. Only one isomer was detected by $^1$H NMR. The crude product was purified by FCC (hexane : ethyl acetate 95 : 5) to provide the *anti* isomer in 70 % yield as a colorless oil. Enantioselectivity was measured by $^1$H NMR in $CDCl_3$ with (*S*)-(+)-TFAE as the shift reagent.

**$[\alpha]^{25}_D$** -191 (c 1.0, chloroform) (96 % ee)

Procedure P4 afforded crude product as a yellowish oil. Ratio of diasteroisomers was measured by $^1$H NMR and was found to be 1 : 24. The crude product was purified by FCC (hexane : ethyl acetate 95 : 5) to provide the *anti* isomer in 49 % yield as a colorless oil.

**$[\alpha]^{25}_D$** -166 (c 0.95, chloroform)

**lit. $[\alpha]^{25}_D$** -96.9 (c 1.0, chloroform) (de > 96)[11]

**$R_f$** 0.52 (hexane : ethyl acetate 1 : 4)

**IR** (KBr)**:** 3534, 2962, 2877, 1737, 1468, 1374, 1223, 1093 $cm^{-1}$

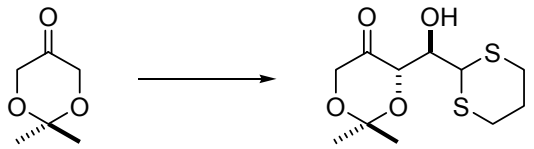
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.25 (dd, $J_1$=1.3 Hz, $J_2$=17.3 Hz, 1H), 4.12 (dd, $J_1$=1.3 Hz, $J_2$=7.9 Hz, 1H), 4.00 (d, $J$=17.3 Hz, 1H), 3.68 (dd, $J_1$=3.5 Hz, $J_2$=7.9 Hz, 1H), 3.09 (br s, 1H), 2.02-1.96 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 0.98 (d, $J$=7.0 Hz, 3H), 0.90 (d, $J$=7.0 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *$\delta$:* 212.4, 101.1, 74.4, 74.0, 66.7, 28.6, 23.9, 23.8, 19.4, 15.4

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 220 ($[M+18]^+$, 100), 203 ($[M+1]^+$, 80), 180 (62), 136 (11), 120 (14)

**HRMS** *m/z* calcd for $C_{10}H_{19}O_4$ 203.1283 (M+H), found 203.1282 (CI)

**4-(*S*)-4-[(*R*)-(1,3-dithian-2-yl)(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one (7c)[12]**




**1a** **7c**

Procedure P1 afforded crude product as a yellowish solid. The ratio of diasteroisomers was measured by $^1$H NMR and was found to be 1 : 41. The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* isomer in 81 % yield as a white solid. Enantioselectivity was measured by $^1$H NMR in $C_6D_6$ with Eu(tfc)$_3$ as a shift reagent.

$[\alpha]^{24}_D$ -77 (c 1.2, chloroform) (66 % ee)
$[\alpha]^{23}_D$ -77.6 (c 1.05, chloroform) (68 % ee)[12]

Procedure P2 afforded crude product as a yellowish solid. Ratio of diasteroisomers was detected by $^1$H NMR and was found to be 1 : 21. The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* isomer in 85 % yield as a white solid. Enantioselectivity was measured by $^1$H NMR in $C_6D_6$ with Eu(tfc)$_3$ as a shift reagent.

$[\alpha]^{23}_D$ -105 (c 0.72, chloroform) (90 % ee)

Procedure P3 afforded crude product as a yellowish solid. Only one isomer was detected by $^1$H NMR. The crude was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* isomer in 83 % yield as a colorless solid. Enantioselectivity was measured by $^1$H NMR in $C_6D_6$ with Eu(tfc)$_3$ as a shift reagent.

$[\alpha]^{25}_D$ -110 (c 1.0, chloroform) (93 % ee)

**Rf** 0.27 (hexane : ethyl acetate 1 : 4)

**mp** 73-75 °C, **lit**.[12] 74-76 °C

**IR** (KBr): 3489, 2986, 2907, 2894, 2833, 1737, 1423, 1375, 1290, 1222, 1164, 1109, 1041, 1003 $cm^{-1}$

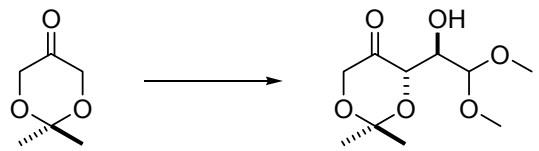
**$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.62 (dd, $J_1$=1.0 Hz, $J_2$=4.0 Hz, 1H), 4.56 (dd, $J_1$=4.0 Hz, $J_2$=7.5 Hz, 1H), 4.46 (dd, $J_1$=1.0 Hz, $J_2$=16.5 Hz, 1H), 4.00 (d, $J$=16.5 Hz, 1H), 3.90 (d, $J$=7.5 Hz, 1H), 3.15 (br s, 1H), 3.05 (m, 1H), 2.85 (m, 1H), 2.57 (m, 1H), 2.51 (m, 1H), 2.06 (m, 2H), 1.51 (s, 3H), 1.47 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.8, 101.1, 75.4, 72.5, 66.8, 43.5, 26.4, 25.4, 25.2, 24.4, 23.4

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 279 ($[M+1]^+$, 100), 221 (85), 149 (12), 119 (87)

**HRMS** *m/z* calcd for $C_{11}H_{18}O_4S_2$ 278.0647 (M), found 278.0639 (EI)

**4-(*S*)-4-[(*R*)-1-hydroxy-2,2-dimethoxyethyl]-2,2-dimethyl-1,3-dioxan-5-one (7h)[12]**



**1a** **7h**

Procedure P1 afforded the crude product as a brown liquid. The ratio of diasteroisomers was measured by $^1$H NMR by integrating the peaks at 4.17 ppm (dd, $J_1$=1.0 Hz, $J_2$=6.8 Hz) and 4.07 ppm (dd, $J_1$=3.1 Hz, $J_2$=6.8 Hz) and was found to be 1 : 8 *syn* to *anti*. The crude product was purified by FCC (hexane : ethyl acetate 7 : 3) to provide the pure compound **7h** in 41 % yield as a pale yellow oil. (The yield refers to the mixture of the *syn* and *anti* isomers). Enantioselectivity was measured by $^1$H NMR in $C_6D_6$ with $Eu(tfc)_3$ as a shift reagent.

**$[\alpha]^{25}_D$** -123 (c 1, chloroform) (91 % ee)
**lit. $[\alpha]^{25}_D$** -121.7 (c 1.05, chloroform) (90 % ee)[12]

Procedure P2 afforded the crude product as a pale yellow oil. The ratio of diasteroisomers was measured by $^1$H NMR by integrating the peaks at 4.17 ppm (dd, $J_1$=1.0 Hz, $J_2$=6.8 Hz) and 4.07 ppm (dd, $J_1$=3.1 Hz, $J_2$=6.8 Hz) and was found to be 1 : 19. The crude product was purified by FCC (hexane : ethyl acetate 7 : 3) to provide the *anti* isomer in 74 % yield as a colorless oil. Enantioselectivity was measured by $^1$H NMR in $C_6D_6$ with $Eu(tfc)_3$ as a shift reagent.

**$[\alpha]^{25}_D$** -123 (c 1, chloroform) (91 % ee)

Procedure P3 afforded the crude product as a pale yellow oil. The ratio of diasteroisomers was measured by $^1$H NMR by integrating the peaks at 4.17 ppm (dd, $J_1$=1.0 Hz, $J_2$=6.8 Hz) and 4.07 ppm (dd, $J_1$=3.1 Hz, $J_2$=6.8 Hz) and was found to be 1

: 5. The crude product was purified by FCC (hexane : ethyl acetate 7: 3) to provide a mixture of the *syn* and *anti* isomers in 70 % combined yield as a pale yellow oil.
**$[\alpha]^{23}_{D}$** -106 (c 0.76, chloroform) (80 % ee)

Procedure P4 afforded the crude product as a brown oil (conversion ca. 80 % by NMR). The ratio of diasteroisomers was measured by $^{1}$H NMR by integrating the peaks at 4.17 ppm (dd, $J_1$=1.0 Hz, $J_2$=6.8 Hz) and 4.07 ppm (dd, $J_1$=3.1 Hz, $J_2$=6.8 Hz) and was found to be 1 : 12. The crude product was purified by FCC (hexane : ethyl acetate 7 : 3) to provide pure compound in 46 % yield as a pale yellow oil. Yield refers to the mixture of *syn* and *anti* isomers.

**$[\alpha]^{25}_{D}$** -110 (c 1.04, chloroform) (83 % ee)

Procedure P5 afforded the crude product as a brown oil (conversion ca. 50 % by NMR). The ratio of diasteroisomers was detected by $^{1}$H NMR by integrating the peaks at 4.17 ppm (dd, $J_1$=1.0 Hz, $J_2$=6.8 Hz) and 4.07 ppm (dd, $J_1$=3.1 Hz, $J_2$=6.8 Hz) and was found to be 1 : 18 *syn* to *anti*. The crude product was purified by FCC (hexane : ethyl acetate 7 : 3) to provide the pure product in 23 % yield as a pale yellow oil. Yield refers to the mixture of *syn* and *anti* isomers.

**$[\alpha]^{25}_{D}$** -44.5 (c 1.1, chloroform) (33 % ee)

**$R_f$** 0.21 (hexane : ethyl acetate 3 : 2)
**IR** (KBr): 3395, 2941, 1747, 1446, 1377, 1193, 1074 cm$^{-1}$
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.65 (d, *J*=6.8 Hz, 1H), 4.44 (dd, $J_1$=1.3 Hz, $J_2$=2.9 Hz, 1H), 4.25 (dd, $J_1$=1.5 Hz, $J_2$=16.7 Hz, 1H), 4.07 (dd, $J_1$=3.1 Hz, $J_2$=6.8 Hz, 1H), 3.99 (*J*=16.7 Hz, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 2.42 (br s, 1H), 1.47 (s, 6H)
**$^{1}$H NMR** (500 MHz, $C_6D_6$) *δ*: 4.78 (d, *J*=7.2 Hz, 1H), 4.50 (m, 1H), ), 4.30 (d, *J*=7.2 Hz, 1H), 4.06 (dd, $J_1$=1.2 Hz, $J_2$=16.2 Hz, 1H), 3.76 (d, *J*=16.2 Hz, 1H), 3.12 (s, 3H), 3.10 (s, 3H), 2.20 (br s, 1H), 1.23 (s, 3H), 1.16 (s, 3H)

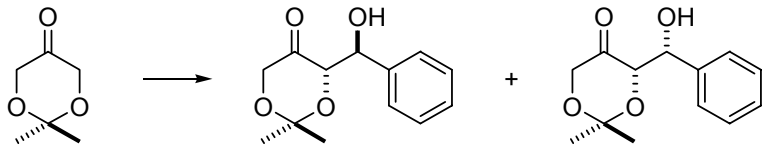
**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 206.5, 103.4, 100.5, 76.3, 71.2, 67.1, 55.4, 54.3, 25.0, 23.0

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 205.9, 104.1, 100.6, 77.4, 72.1, 67.5, 55.0, 53.7, 25.3, 23.1

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 252 ($[M+18]^+$, 27), 220 (75), 203 (65), 188 (100), 168 (31), 75 (62)

**HRMS** *m/z* calcd for $C_{10}H_{18}O_6$ 252.1447 ($M+NH_4$), found 252.1443 (CI)

**4-(*S*)-4-[(*S*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxan-5-one (7e) and 4-(*S*)-4-[(*R*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxan-5-one (8e)[11]**




Procedure P1 (0.50 mmol scale) afforded the crude product as a yellowish oil. Diastereoselectivity of the reaction was determined on the crude reaction mixture by integration of $^1$H NMR peaks at 5.20 ppm (*J*=2.9 Hz) and 4.87 ppm (*J*=7.8 Hz) and was found to be 1 : 1.8 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* aldol (42.5 mg, 0.180 mmol) in 36 % yield as a yellowish oil and the *syn* isomer (22 mg, 9.1 $10^{-2}$ mmol) in 18 % yield as a yellowish oil. Enantioselectivity was measured by $^1$H NMR in deuterated chloroform with $Eu(tfc)_3$ as a shift reagent and was found to be 68 %.

**$[\alpha]^{26}_D$** -92 (c 1.23, chloroform) (68 % ee)

Procedure P2 (0.50 mmol scale) afforded the crude product as yellowish oil. Diastereoselectivity of the reaction was determined by integration of $^1$H NMR peaks at 5.20 ppm (*J*=2.9 Hz) and 4.87 ppm (*J*=7.8 Hz) and was found to be 1 : 2.4 (*syn* : *anti*).The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* product (71 mg, 0.30 mmol) in 60 % yield as a yellowish oil and the *syn* isomer (29 mg, 0.12 mmol) in 25 % yield as a yellowish oil. Enantioselectivity was measured by $^1$H NMR in deuterated chloroform with $Eu(tfc)_3$ as a shift reagent and was found to be 86 %.

**$[\alpha]^{25}_D$** -111 (c 1.0, chloroform) (86 % ee)

Procedure P3 (0.50 mmol scale) afforded the crude product as a yellowish solid. Diastereoselectivity of the reaction was determined by integration of $^1$H NMR peaks at 5.20 ppm ($J$=2.9 Hz) and 4.87 ppm ($J$=7.5 Hz) and was found to be 1 : 4.6 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* (64.0 mg, 0.271 mmol) in 54 % yield as a yellowish oil and the *syn* isomer (13 mg, 5.5 $10^{-2}$ mmol) in 11 % yield as a yellowish oil. Enantioselectivity was measured by $^1$H NMR in deuterated benzene with (*S*)-(+)-TFAE as a shift reagent and was found to be 86 %.

**$[\alpha]^{25}_D$** -110 (c 0.7, chloroform) (86 % ee)
**$[\alpha]^{25}_D$** -121.2 (c 1, chloroform) (de .96)[11]

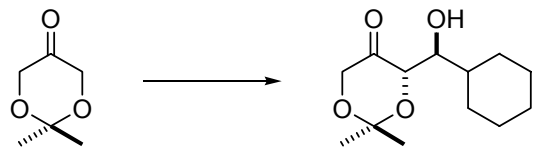
**7e**

**$R_f$** 0.32 (hexane : ethyl acetate 7 : 3)
**IR** (KBr): 3492, 1740 cm$^{-1}$
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.42-7.27 (m, 5H), 4.88 (d, $J$=7.8 Hz, 1H), 4.32 (d, $J$=7.8 Hz, 1H), 4.22 (dd, $J_1$=1.3 Hz, $J_2$=17.5 Hz, 1H), 4.02 (d, $J$=17.5 Hz, 1H), 3.57 (br s, 1H), 1.35 (s, 3H), 1.23 (s, 3H)
**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 211.2, 139.5, 128.3, 127.3, 101.4, 76.4, 73.0, 66.9, 23.9, 23.4

**8e**

**$R_f$** 0.26 (hexane : ethyl acetate 7 : 3)
**IR** (KBr): 3444, 1722 cm$^{-1}$
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.49-7.27 (m, 5H), 5.20 (d, $J$=2.9 Hz, 1H), 4.43 (d, $J$=2.9 Hz, 1H), 4.26 (d, $J$=17.0 Hz, 1H), 4.00 (dd, $J_1$=1.3 Hz, $J_2$=17.0 Hz, 1H), 1.45 (s, 3H), 1.33 (s, 3H)
**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 207.8, 140.3, 130.3, 128.6, 128.4, 128.0, 126.7, 101.2, 78.3, 71.5, 67.3, 24.4, 23.5

**4-(*S*)-4-[(*S*)-cyclohexyl(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one (7k)[11]**



**1a** **7k**

Procedure P1 afforded the crude product as yellowish oil. Diastereoselectivity of the reaction was determined by integration of $^1$H NMR peaks at 4.94 ppm ($J$=5.4 Hz) and 4.18 ppm (dd, $J_1$=1.5 Hz, $J_2$=7.8 Hz) and was found to be 1 : 25 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 5 : 95) to provide the *anti* isomer in 80 % yield as a colorless oil.

Procedure P2 afforded the crude product as yellowish oil. Diastereoselectivity of the reaction was determined by $^1$H NMR and was found to be 1 : 99 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 5 : 95) to provide the *anti* isomer in 74 % yield as a colorless oil.

Procedure P3 afforded the crude product as yellowish oil. Diastereoselectivity of the reaction was determined by $^1$H NMR and was found to be 1 : 99 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 5 : 95) to provide the mixture of the *anti* and *syn* isomers in 64 % combined yield as a colorless oil.

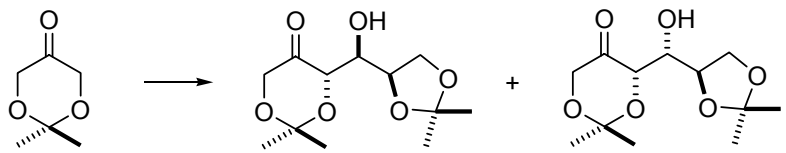
**Rf** 0.41 (hexanes : ethyl acetate 4 : 1)

**IR** (KBr): 3405, 1735cm$^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.25 (dd, $J_1$=1.4 Hz, $J_2$=17.4 Hz, 1H), 4.18 (dd, $J_1$=1.4 Hz, $J_2$=7.8 Hz, 1H), 4.00 (d, $J$=17.4 Hz, 1H), 3.67 (ddd, $J_1$=2.9 Hz, $J_2$=3.4 Hz, $J_3$=7.8 Hz, 1H), 2.97 (d, $J$=2.9 Hz, 1H), 1.75-1.49 (m, 6H), 1.45 (s, 3H), 1.41 (s, 3H), 1.39-1.12 (m, 5H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 212.5, 101.1, 74.4, 73.6, 66.9, 38.7, 29.7, 26.7, 26.6, 26.5, 26.3, 24.0, 23.8

**(-)-1,3 : 5,6-di-O-Isopropylidene-D-tagatose (7d)**[7]




Procedure P1 (5.0 mmol scale) afforded the crude product as a yellowish liquid. Diastereoselectivity of the reaction was determined by integration of $^{1}$H NMR peaks and was found to be 1 : 20 **8d** to **7d**. The crude product was purified by FCC (hexane : ethyl acetate 15 %) to provide **7d** (0.72 g, 2.7 mmol) in 55 % yield as a white solid.

Procedure P2 (8.7 mmol scale) afforded the crude product as a yellowish solid. Diastereoselectivity of the reaction was determined by integration of $^{1}$H NMR peaks and was found to be 1:4 (*syn* : *anti*). The crude product was purified by FCC (15 % hexane : ethyl acetate) to provide the *anti* isomer **7d** (1.2 g, 4.4 mmol, 51 %) as a white solid and *syn* isomer **8d** (0.31 g, 1.2 mmol) in 14 % as a colorless liquid.

**7d**

**m.p**. 102-103**, lit.**[7] 103-105 °C

**$[\alpha]^{24}_{D}$** -148 (c 0.9, chloroform) **lit. $[\alpha]^{25}_{D}$** -167 (c 1.1, chloroform)[7]

**Rf** 0.20 (hexane : ethyl acetate 7 : 3)

**IR** (KBr): 3473, 1745 cm$^{-1}$

**$^{1}$H NMR** (500 MHz, $C_6D_6$) *δ:* 4.30 (dd, $J_1$=1.2 Hz, $J_2$=7.6 Hz, 1H), 4.28 (ddd, $J_1$=3.3 Hz, $J_2$=6.8 Hz, $J_3$=7.5 Hz, 1H), 3.98 (d, $J_1$=7.5 Hz, $J_2$=7.8 Hz, 1H), 3.79 (dd, $J_1$=1,2 Hz, $J_2$=17.4 Hz, 1H), 3.78 (dd, $J_1$=6.8 Hz, $J_2$=7.8 Hz, 1H), 3.67 (ddd, $J_1$=3.3 Hz, $J_2$=3.3 Hz, $J_3$=7.6 Hz, 1H), 3.60 (d, $J$=17.4 Hz, 1H), 3.15 (d, $J$=3.3 Hz, 1H), 1.48 (s, 3H), 1.36 (s, 3H), 1.24 (s, 3H), 1.09 (s, 3H)

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.28-4.23 (m, 3H), 4.03 (d, *J*=17.5 Hz, 1H), 3.97 (dd, $J_1$=8.0 Hz, $J_2$=8.0 Hz, 1H), 3.87-3.81 (m, 2H), 3.14 (br s, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H)

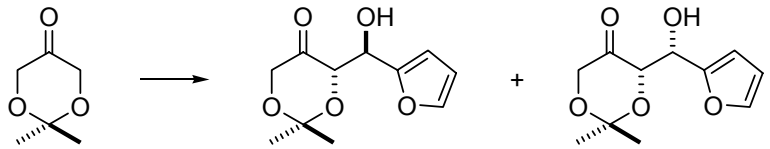
**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 210.8, 109.7, 101.5, 75.7, 74.1, 70.2, 66.9, 65.8, 26.8, 26.5, 23.9, 23.8

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 210.5, 109.4, 101.5, 75.4, 73.7, 70.3, 66.9, 65.8, 26.5, 25.8, 23.9, 23.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 278 ($[M+18]^+$, 100), 261 (26), 243 (53), 220 (98), 148 (28)

**HRMS** *m/z* calcd for $C_{12}H_{20}O_6$ 278.1604 ($M+NH_4$), found 278.1611 (CI)

**4-(*S*)-4-[(*R*)-furan-2-yl(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one (7g)**
**4-(*S*)-4-[(*S*)-furan-2-yl(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one (8g)**[13]




Procedure P1 afforded the crude product as a brown oil. Diastereoselectivity of the reaction was determined by integration of $^1$H NMR ($CDCl_3$) peaks at 5.21 ppm (*J*=2.9 Hz) and 4.97 ppm (*J*=7.0 Hz) and was found to be 1 : 2 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the mixture of *syn* and *anti* isomer in 19 % yield as a brown liquid.

Procedure P2 afforded the crude product as a brown oil. Diastereoselectivity of the reaction was determined by integration of $^1$H NMR ($CDCl_3$) peaks at 5.21 ppm (*J*=2.9 Hz) and 4.97 ppm (*J*=7.0 Hz) and was found to be 1 : 3 (*syn* : *anti*). The crude product was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the mixture of *syn* and *anti* isomer in 45 % yield as a brown liquid.

In both cases determination of optical rotation values was not possible due to the fact that the *syn* and *anti* isomers could not be separated. All the spectral date were obtained on the mixture of 2 isomers and analyzed as a mixture.

**7g**

**$R_f$** 0.22 (hexane : ethyl acetate 7 : 3)
**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 7.07 (s, 1H), 6.25 (m, 1H), 6.05 (m, 1H), 5.01 (d, *J*=6.7 Hz, 1H), 4.45 (dd, $J_1$=1.2 Hz, $J_2$=6.7 Hz, 1H), 3.79 (dd, $J_1$=1.2 Hz, $J_2$=17.3 Hz, 1H), 3.60 (d, *J*=17.3 Hz, 1H) 3.19 ( br s, 1H), 1.16 (s, 3H), 1.03 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 206.4, 153.9, 142.5, 110.8, 108.7, 101.4, 75.7, 67.6, 66.9, 23.9, 23.5

**8g**

**$R_f$** 0.22 (hexane : ethyl acetate 7 : 3)

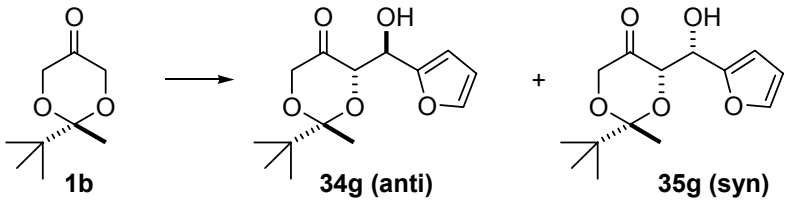
**IR** (KBr): done on the mixture of **7g** and **8g:** 3462, 2967, 2911, 2879, 1739, 1703, 1593, 1474, 1379, 1348, 1274, 1164, 1087, 922, 736 $cm^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 7.04 (s, 1H), 6.20 (m, 1H), 6.05 (m, 1H), 5.31 (d, *J*=2.3 Hz, 1H), 4.32 (dd, $J_1$=1.4 Hz, $J_2$=2.3 Hz, 1H), 3.87 (dd, $J_1$=1.4 Hz, $J_2$=16.7 Hz, 1H), 3.68 (d, *J*=16.7 Hz, 1H) 2.60 ( br s, 1H), 1.08 (s, 6H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) ***δ:*** 209.3, 154.8, 142.3, 110.9, 107.8, 101.1, 76.8, 67.4, 66.9, 24.4, 23.6

**(2*R*,4*S*)-2-(*tert*-Butyl)-4-[(*R*)-furan-2-yl(hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (34g)**

**(2*R*,4*S*)-2-(*tert*-Butyl)-4-[(*S*)-furan-2-yl(hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (35g)**




Procedure P1 afforded crude product as brown oil. Diastereoselectivity of reaction was determined by integration of $^1$H NMR ($CDCl_3$) peaks at 4.57 ppm ($J$=2.6 Hz) and 4.61 ppm ($J_1$=1.0 Hz, $J_2$=5.5 Hz) and was found to be 1 : 10 (*syn* : *anti*). The crude was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* isomer in 35 % yield as brown liquid.

Procedure P2 afforded crude product as brown oil. Diastereoselectivity of reaction was determined by integration of $^1$H NMR ($CDCl_3$) peaks at 4.57 ppm ($J$=2.6 Hz) and 4.61 ppm ($J_1$=1.0 Hz, $J_2$=5.5 Hz) and was found to be 1 : 13 (*syn* : *anti*). The crude was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the mixture of *syn* and *anti* isomer in 65 % yield as brown liquid.

**34g**

**IR** (KBr): 3460, 2962, 2915, 2877, 1741, 1597, 1483, 1394, 1378, 1278, 1165, 1012 $cm^{-1}$

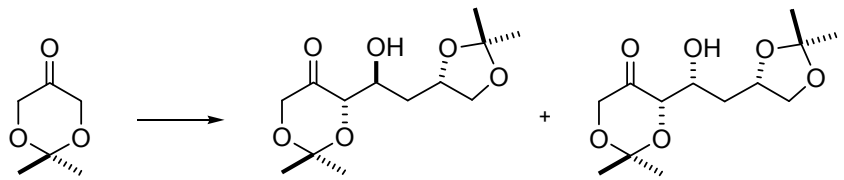
**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 7.03 (s, 1H), 6.25 (d, $J$=2.9 Hz, 1H), 6.03 (dd, $J_1$=1.9 Hz, $J_2$=2.9 Hz, 1H), 5.10 (d, $J$=5.0 Hz, 1H), 4.41 (dd, $J_1$=1.0 Hz, $J_2$=5.0 Hz, 1H), 4.02 (dd, $J_1$ =1.0 Hz, $J_2$=18.4 Hz, 1H), 3.82 (d, $J$=18.4 Hz, 1H) 2.83 (br s, 1H), 0.96 (s, 3H), 0.90 (s, 9H)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 206.6, 153.7, 142.4, 110.8, 108.3, 103.9, 78.8, 69.6, 69.2, 40.4, 25.4, 15.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 269 ($[M+1]^+$, 34), 251 (58), 193 (34), 173 (100), 114 (32)

**HRMS** *m/z* calcd for $C_{14}H_{20}O_5$ 269.1389 (M+H), found 269.1387 (CI)

**Protected 4-deoxy-heptose (7j)**




Procedure P2 afforded the crude product as a yellow oil. Diastereoselectivity of the reaction was determined by $^{1}$H NMR ($CDCl_3$) and was found to be 1 : 1.5 (*syn* : *anti*). The efforts to separate the products by FCC (hexane : ethyl acetate) provided only partial separation of the mixture and the product was tentatively assigned as an *anti* – *anti* diastereoisomer.

## 7j

**IR** (KBr): 3377, 2959, 2932, 1741, 1379, 1259, 1222, 1063, 801 $cm^{-1}$

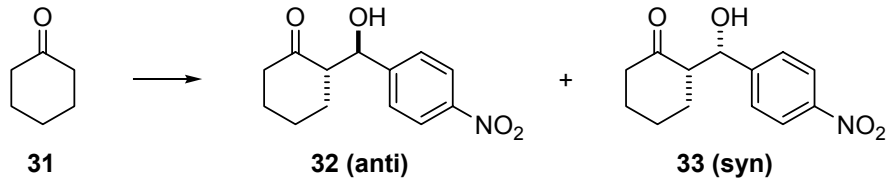
**$^{1}$H NMR** (500 MHz, $C_6D_6$) *δ:* 4.36-4.29 (m, 1H), 4.24 (dd, $J_1$=1.5 Hz, $J_2$=6.1 Hz, 1H), 4.23 (dd, $J_1$=1.5 Hz, $J_2$=17.2 Hz, 1H), 4.11-4.05 (m, 2H), 4.00 (d, $J$=17.2 Hz, 1H), 3.55 (dd, $J_1$=7.8 Hz, $J_2$=7.8 Hz, 1H), 3.38 (d, $J$=2.5 Hz, 1H) 1.95-1.88 (m, 1H), 1.79-1.74 (m, 1H), 1.47 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 210.6, 109.4, 101.4, 76.2, 74.1, 69.8, 69.2, 67.0, 35.3, 27.1, 26.0, 24.1, 23.8

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 292 ($[M+18]^+$, 59), 275 ($[M+1]^+$, 20), 252 (35), 234 (81), 217 (100), 202 (16), 194 (78), 145 (19), 131 (12), 58 (17)

**HRMS** *m/z* calcd for $C_{13}H_{22}O_6$ 275.1495 (M+H), found 275.1492(CI)

**2-(*S*)-2-[(*R*)-hydroxy(4-nitrophenyl)methyl]cyclohexanone (32) and**
**2-(*S*)-2-[(*S*)-hydroxy(4-nitrophenyl)methyl]cyclohexanone (33)[14]**



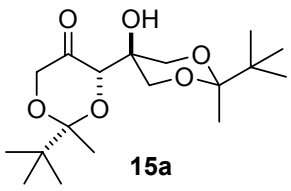

**31** **32 (anti)** **33 (syn)**

Procedure P3 (0.50 mmol scale) afforded the crude product as a yellow solid. Diastereoselectivity of the reaction was determined by $^1$H NMR ($CDCl_3$) by integration of characteristic peaks at 5.43 ppm (*J*=2.2 Hz) and 4.85 ppm (*J*=8.4 Hz) and was found to be 1 : 15.2 (*syn* : *anti*). The crude reaction mixture was purified by FCC (20 % ethyl acetate in hexane) to provide *anti* product (**32**) as a pale yellow solid (0.10 g, 0.42 mmol, 83 %).

**32**

**$R_f$** 0.30 (hexane : ethyl acetate 3 : 2)
**IR** (KBr): 3514, 2939, 2864, 1699, 1604, 1518, 1346, 1313, 856 $cm^{-1}$
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 8.16 (d, *J*=8.7 Hz, 2H), 7.46 (d, *J*=8.7 Hz, 2H), 4.85 (d, *J*=8.4 Hz, 1H), 2.58-2.51 (m, 1H), 2.48-2.41 (m, 1H), 2.36-2.27 (m, 1H), 2.10-2.03 (m, 1H) 1.81-1.74 (m, 1H), 1.71-1.45 (m, 1H), 1.39-1.28 (m, 1H)
**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 214.9, 148.6, 147.8, 128.1, 123.8, 74.2, 57.4, 42.9, 31.0, 27.9, 24.9

**2-*tert* –Butyl-2-methyl -1,3-dioxan-5-one dimer (15a)**




**15a**

Compound 15a was frequently isolated by-product in proline catalyzed aldol reaction.

**$R_f$** 0.61 (hexane : ethyl acetate 3 : 2)

**IR** (KBr): 3485, 2962, 2887, 1731, 1484, 1376, 1260, 1154, 1105, 1164, 1042, 918, 874, $cm^{-1}$

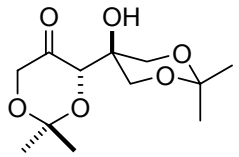
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.73 (dd, $J_1$=1.0 Hz, $J_2$=1.3 Hz, 1H), 4.28 (dd, $J_1$=1.3 Hz, $J_2$=17.8 Hz, 1H), 4.20 (dd, $J_1$=2.8 Hz, $J_2$=11.8 Hz, 1H), 4.18 (dd, $J_1$=1.0 Hz, $J_2$=17.8 Hz, 1H), 4.05 (dd, $J_1$=2.8 Hz, $J_2$=11.1 Hz, 1H), 3.73 (d, $J$=11.8 Hz, 1H), 3.57 (d, $J$=11.1 Hz, 1H), 2.40 (br s, 1H), 1.41 (s, 3H) 1.37 (s, 3H), 1.05 (s, 9H), 0.95 (s, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.6, 104.2, 102.5, 75.6, 70.8, 69.3, 64.7, 64.0, 40.6, 39.5, 25.5, 25.0, 16.9, 12.0,

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 345 ($[M+1]^+$, 96), 287 (13), 262 (100), 245 (19), 173 (89), 118 (13)

**HRMS** *m/z* calcd for $C_{18}H_{32}O_6$ 345.2277 (M+H), found 345.2268 (CI)

**4-(*S*)-[5-Hydroxy-2,2,-dimethyl-1,3-dioxan-5-yl]-2,2-dimethyl-1,3-dioxan-5-one (15)**[7]



**15**

Compound **15** was frequently isolated by-product in proline catalyzed aldol reaction. Deliberately run reaction of dioxanone under organocatalytic conditions in absence of the electrophile led to formation of **15** in 40 – 50 % yield. Dimer was also often observed in lithium enolate mediated aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one upon aqueous quench or in unsuccessful attempts for alkylation reaction.

**$R_f$** 0.32 (hexane : ethyl acetate 3 : 2)

**IR** (KBr): 3448, 2987, 2942, 2877, 1746, 1445, 1370, 1220, 1150, 1070, 829, $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.44 (s, 1H), 4.23 (d, *J*=17.3 Hz, 1H), 4.09 (d, *J*=12.0 Hz, 1H), 3.99 (d, *J*=11.7 Hz, 1H), 3.98 (d, *J*=17.3 Hz, 1H), 3.81 (d, *J*=12.0 Hz, 1H), 3.62 (d, *J*=11.7 Hz, 1H), 2.83 (br s, 1H), 1.45 (s, 3H) 1.44 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.7, 101.5, 98.7, 74.1, 69.0, 67.6, 65.5, 64.8, 24.1, 23.7, 23.6, 23.5

### 3.6. Protection of dioxanone aldol products.

**General experimental procedures for TBS or TIPS protection reaction**

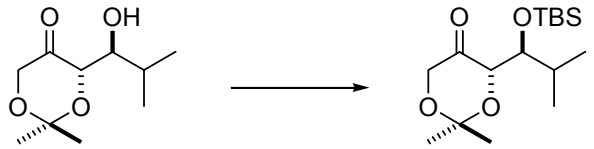
Procedure S1. TIPS protection in the presence of 2,6-lutidine[15]

To a cold solution of β-hydroxydioxanone (1.0 eq) in dry THF (5.0 mL/1.0 mmol) were added dropwise 2,6-lutidine (2.0 eq) at 0 °C followed by TIPSOTf (1.2 - 1.5 eq). The reaction was warmed up to rt and stirred until no starting material was detected by TLC (usually 1 - 3 h depending on the substrate. Occasionally the reaction required overnight stirring). The saturated solution of sodium bicarbonate was then added, the mixture was extracted with dichloromethane (x 3) and the combined organic layers were washed with saturated solution of sodium chloride, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography ($SiO_2$, hexane : ethyl acetate 0 - 10 %) to afford the TIPS-protected products.

Procedure S2. TBS protection in the presence of 2,6-lutidine[16]

To a cold solution of β-hydroxydioxanone (1.0 eq) in dry THF (5.0 mL/1.0 mmol) were added dropwise 2,6-lutidine (2.0 eq) at -78 °C followed by TBSOTf (1.2 - 1.5 eq). The reaction was stirred at -78 °C until no starting material was detected by TLC (usually 1-3 h depending on the substrate). The saturated solution of sodium bicarbonate was then added, extracted with dichloromethane (x 3) and the combined organic layers were washed with saturated solution of sodium chloride, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography ($SiO_2$, hexane : ethyl acetate 0 - 10 %) to afford the TBS-protected products.

**4-(*S*)-4-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl]-2,2-dimethyl-1,3-dioxan-5-one (56)**




**7f** **56**

Procedure S2 afforded the crude product which was purified by FCC (hexane : ethyl acetate 3 : 97). The silylated product **56** was obtained as a colorless liquid in 91 % yield.

**$[\alpha]^{24}_{D}$** -138 (c 1, chloroform)

**$R_f$** 0.48 (hexane : ethyl acetate 9 : 1)

**$R_f$** 0.58 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 2936, 2851, 1747, 1461, 1376, 1244, 1116, 1074, 992, 826, 775

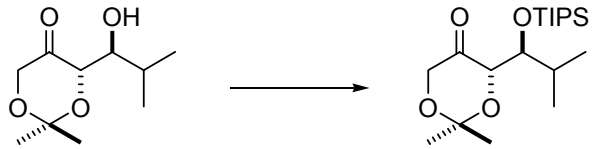
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.27 (dd, $J_1$=1.1 Hz, $J_2$=2.4 Hz, 1H), 4.22 (dd, $J_1$=1.1 Hz, $J_2$=16.4 Hz, 1H), 3.90 (d, $J_1$=16.4 Hz, 1H), 3.77 (dd, $J_1$=2.4 Hz, $J_2$=7.3 Hz, 1H), 2.04-2.00 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 0.91 (d, *J*=6.8 Hz, 1H), 0.86 (s, 9H), 0.82 (d, *J*=6.8 Hz, 1H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) ***δ:*** 207.9, 100.8, 78.4, 77.5, 67.3, 30.9, 26.2, 24.6, 23.5, 20.0, 19.6, 18.4, -3.9, -4.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 334 ($[M+18]^+$, 16), 317 ($[M]^+$+1, 53), 178 (100), 132 (72)

**HRMS** *m/z* calcd for $C_{16}H_{32}O_4Si$ 317.2148 (M+H), found 317.2153 (CI)

**4-(*S*)-4-[(*S*)-1-(triisopropylsilyloxy)-2-methylpropyl]-2,2-dimethyl-1,3-dioxan-5-one (51f)**




**7f** **51f**

Procedure S1 afforded the crude product which was purified by FCC (hexane : ethyl acetate 3 : 97). The silylated product (TIPS protected **51f**) was obtained as a colorless liquid in 90 % yield.

**$[\alpha]^{26}_{D}$** -109 (c 1, chloroform)

**$R_f$** 0.62 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 2943, 2867, 1747, 1464, 1224, 1163, 1093, 1066, 883, 677 $cm^{-1}$

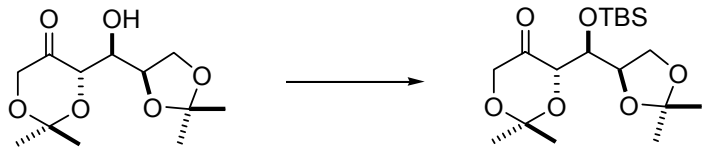
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.36 (dd, $J_1$=1.3 Hz, $J_2$=2.3 Hz, 1H), 4.25 (dd, $J_1$=1.3 Hz, $J_2$=16.6 Hz, 1H), 4.09 (dd, $J_1$=2.3 Hz, $J_2$=6.5 Hz, 1H), 3.93 (d, *J*=16.6 Hz, 1H), 2.03-1.99 (m, 1H), 1.44 (s, 6H), 1.20-1.07 (m, 18H), 0.96 (d, *J*=6.8 Hz, 1H), 0.85 (d, *J*=6.8 Hz, 1H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) ***δ:*** 207.9, 100.8, 79.4, 77.1, 67.2, 31.9, 24.6, 23.5, 19.9, 19.5, 18.5, 13.2

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 359 ($[M+1]^+$, 28), 315 (7), 229 (100), 185 (19)

**HRMS** *m/z* calcd for $C_{19}H_{38}O_4Si$ 359.2618 (M+H), found 359.2618 (CI)

**4-(*S*)-4-[(*S*)-(tert-Butyldimethylsilyloxy)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)]-2,2-dimethyl-1,3-dioxan-5-one (51d)**




**7d** **51d**

*Reaction was done according to the procedure S2*

To a cold solution of **7d** (0.56 g, 2.1 mmol, 1.0 eq) in dry THF (11 mL) were added dropwise 2,6-lutidine (0.50 mL, 4.3 mmol, 2.0 eq) followed by TBSOTf (0.60 mL, 4.6 mmol, 1.2 eq). The reaction was stirred at -78 °C until no starting material was detected by TLC (1 h). The saturated solution of sodium bicarbonate was then added, extracted with dichloromethane (x 3) and the combined organic layers were washed with saturated solution of sodium chloride, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FCC ($SiO_2$, hexane : ethyl acetate 95 : 5) to afford the TBS-protected product **51d** (0.77 g, 2.0 mmol) as a colorless liquid in 95 % yield.

**$[\alpha]^{24}_D$** -50 (c 1.06, chloroform)

**$R_f$** 0.49 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 1747 $cm^{-1}$

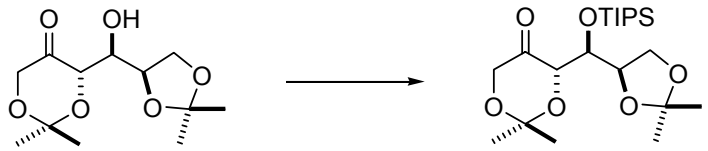
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.29 (ddd, $J_1$=6.4 Hz, $J_2$=8.1 Hz, $J_3$=8.1 Hz, 1H), 4.20 (dd, $J_1$=1.3 Hz, $J_2$=16.5 Hz, 1H), 4.07 (m, 2H), 3.93 (d, $J$=16.5 Hz, 1H), 3.94 (dd, $J_1$=6.4 Hz, $J_2$ =8.1 Hz, 1H), 3.61 (dd, $J_1$=8.1 Hz, $J_2$=8.1 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 0.84 (s, 9H), 0.07 (s, 6H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 206.8, 109.2, 100.7, 77.7, 77.3, 74.4, 67.6, 66.3, 26.8, 26.0, 25.7, 24.9, 23.3, 18.4, -4.2, -4.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 392 ($[M+18]^+$, 23), 375 ($[M+1]^+$, 100 ), 317 (46), 259 (7), 91 (12)

**HRMS** *m/z* calcd for $C_{18}H_{34}O_6Si$ 375.2203 (M+H), found 375.2209 (CI)

**4-(*S*)-4-((*S*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)(triisopropylsilyloxy)methyl)]-2,2-dimethyl-1,3-dioxan-5-one (51d)**




**7d** **51d**

*Reaction was done according to the procedure S1*

To the stirred solution (0 °C) of **7d** (0.14 g, 0.55 mmol, 1.0 eq) in dry THF (3 mL) were added dropwise 2,6-lutidine (0.12 g, 0.13 mL, 1.1 mmol, 2.0 eq) followed by TIPSOTf (0.2 g, 0.18 mL, 0.66 mmol, 1.2 eq). The reaction was stirred at 0 °C until no starting material was detected by TLC. Then saturated solution of $NaHCO_3$ was added, extracted with $CH_2Cl_2$ (x 3) and the combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FCC ($SiO_2$, hexane: ethyl acetate 97: 7) to afford the TIPS - protected product **51d** (0.22 g, 0.53 mmol) as a colourless oil in 96 % yield.

**$[\alpha]^{24}_D$** -64 (c 1.19, chloroform)

**$R_f$** 0.31 (hexane : ethyl acetate 9 : 1)

**IR** (KBr): 1751 $cm^{-1}$

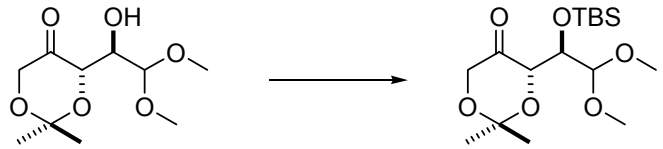
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.43 (dd, $J_1$=1.8 Hz, $J_2$=7.3 Hz, 1H), 4.33 (ddd, $J_1$=6.4 Hz, $J_2$=7.3 Hz, $J_3$=8.5 Hz, 1H), 4.25 (dd, $J_1$=1.5 Hz, $J_2$=16.1 Hz, 1H), 4.23 (dd, $J_1$=1.5 Hz, $J_2$=1.8 Hz, 1H), 3.93 (d, $J$=16.1 Hz, 1H), 3.91 (dd, $J_1$=6.4 Hz, $J_2$=8.2 Hz, 1H), 3.76 (dd, $J_1$=8.2 Hz, $J_2$=8.5 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.56-1.07 (m, 3H), 1.07-1.01 (m, 18H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 206.7, 109.3, 101.7, 78.6, 77.2, 73.5, 67.3, 66.3, 26.7, 25.6, 24.8, 23.2, 18.32, 18.29, 12.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 434 ($[M+18]^+$, 31), 417 ($[M+1]^+$, 100 ), 376 (21), 359 (91), 318 (26), 257 (23), 185 (27), 148 (14), 58 (40)

**HRMS** *m/z* calcd for $C_{21}H_{40}O_6Si$ 417.2672 (M+H), found 417.2665 (CI)

**4-(*S*)-4-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,2-dimethoxyethyl]-2,2-dimethyl-1,3-dioxan-5-one (51h)[13]**




**7h** **51h**

*Reaction was done according to the procedure S2*

To a cold solution of **7h** (0.89 g, 3.8 mmol, 1.0 eq) in dry THF (20 mL) were added dropwise 2,6-lutidine (0.89 mL, 7.7 mmol, 2.0 eq) followed by TBSOTf (1.1 mL, 4.6 mmol, 1.2 eq). The reaction was stirred at -78 °C until no starting material was detected by TLC (1 h). Then saturated solution of sodium hydrocarbonate was added, extracted with dichloromethane (x 3) and the combined organic layers were washed with saturated solution of sodium chloride, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FCC ($SiO_2$, hexane : ethyl acetate 95 : 5) to afford the TBS-protected product **51h** (1.2 g, 3.5 mmol) as colorless liquid in 93 % yield.

**$[\alpha]^{25}_D$** -73 (c 1.07, chloroform), **$[\alpha]^{25}_D$** -88.3 (c 0.69, methanol)[13]

**IR** (KBr): 2943, 2867, 1747, 1464, 1224, 1163, 1093 $cm^{-1}$

**$R_f$** 0.48 (hexane : ethyl acetate 4 : 1)

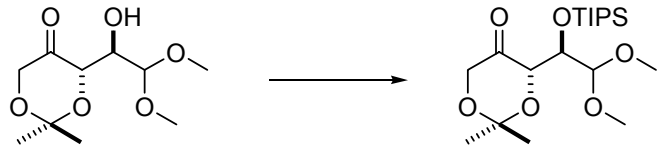
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.29 (ddd, $J_1$=6.4 Hz, $J_2$=8.1 Hz, $J_3$=8.1 Hz, 1H), 4.20 (dd, $J_1$=1.3 Hz, $J_2$=16.5 Hz, 1H), 4.07 (m, 2H), 3.93 (d, $J$=16.5 Hz, 1H), 3.94 (dd, $J_1$=6.4 Hz, $J_2$=8.1 Hz, 1H), 3.61 (dd, $J_1$=8.1 Hz, $J_2$=8.1 Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 0.84 (s, 9H), 0.07 (s, 6H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:*206.8, 109.2, 100.7, 77.7, 77.3, 74.4, 67.6, 66.2, 26.8, 26.0, 25.7, 24.9, 23.3, 18.4, -4.2, -4.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 366 ($[M+18]^+$, 60), 348 (5), 334 (100), 317 (52), 302 (33), 266 (37), 219 (20), 75 (83)

**HRMS** *m/z* calcd for $C_{16}H_{32}O_6Si$ 366.2312 ($M+NH_4$), found 366.2317 (CI)

**4-(*S*)-4-[(*R*)-1-(triisopropylsilyloxy)-2,2-dimethoxyethyl]-2,2-dimethyl-1,3-dioxan-5-one (51h)**




*Reaction was done based on modified procedure S1*

To a cold solution of **7h** (1.3 g, 5.5 mmol, 1.0 eq) in dry THF (10 mL) were added dropwise 2,6-lutidine (1.3 mL, 11 mmol, 2.0 eq) at -78 °C followed by TIPSOTf (2.2 mL, 8.0 mmol, 1.5 eq). The reaction was warmed up to 0 °C and stirred until no starting material was detected by TLC (1 h). Then saturated solution of sodium hydrocarbonate was added, extracted with dichloromethane (x 3) and the combined organic layers were washed with saturated solution of sodium chloride, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FCC ($SiO_2$, hexane : ethyl acetate 95 : 5) to afford the TIPS-protected product **51h** (2.1 g, 5.3 mmol) as colorless liquid in 97 % yield.

**$[\alpha]^{24}_D$** -67 (c 1.09, benzene)

**$R_f$** 0.48 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 2942, 2866, 1749, 1464, 1224, 1169, 999, 882, 677 $cm^{-1}$

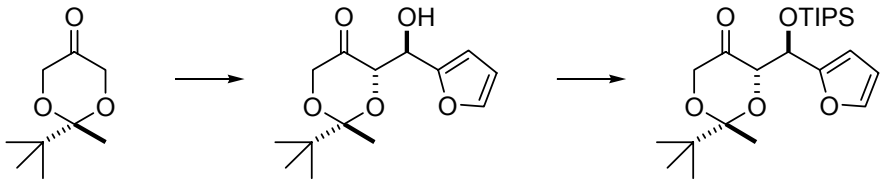
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.52 (d, *J*=7.3 Hz, 1H), 4.34 (d, $J_1$=1.0 Hz, 1H), 4.27 (dd, $J_1$=1.0 Hz, $J_2$=4.3 Hz, 1H), 4.20 (dd, $J_1$=1.0 Hz, $J_2$=16.0 Hz, 1H), 3.87 (d, *J*=16.0 Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.08-1.00 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 205.5, 105.8, 100.3, 78.8, 73.6, 67.0, 55.7, 55.6, 25.2, 23.0, 18.2, 18.1, 17.9, 12.7, 12.5

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 408 ($[M+18]^+$, 42), 376 (82), 359 (100), 344 (48), 315 (21), 257 (21), 185 (26),75 (54)

**HRMS** *m/z* calcd for $C_{19}H_{38}O_6Si$ 408.2781 ($M+NH_4$), found 408.2792 (CI)

**(2R,4S)-2-*tert*-Butyl-4-[(*R*)-furan-2-yl(triisopropylsilyloxy)methyl]-2-methyl-1,3-dioxan-5-one (63g)**




**1b** **34g (anti)** **63g**

Dioxanone **1b** (65 mg, 0.50 mmol, 1.0 eq) and furan-2-carbaldehyde (**2g**) (48 mg, 0.5 mmol, 1.0 eq) were added to a flame-dried vial charged with (*S*)-proline (17 mg, 0.15 mmol, 0.3 eq) and LiCl (21 mg, 0.50 mmol, 1.0 eq). Dry DMSO (0.30 mL) was added; the vial was flushed with nitrogen and stored in a refrigerator at 4 °C for 3 d. The reaction was then quenched with sat. $NH_4Cl$ solution (5 mL) and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried with $MgSO_4$, concentrated and used for next step without purification.

To a cold solution of crude β-hydroxydioxanone (0.11 g, 0.39 mmol, 1.0 eq) in dry THF (3 mL) were added dropwise 2,6-lutidine (0.090 mL, 85 mg, 0.79 mmol, 2.0 eq) at -78 °C followed by TIPSOTf (0.17 g, 0.15 mL, 0.55 mmol, 1.4 eq). The reaction was warmed up to 0 °C and stirred until no starting material was detected by TLC (2 h). Then saturated solution of $NaHCO_3$ was added, extracted with $CH_2Cl_2$ (x 3) and the combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The diastereoisomer ratio was measured by $^1H$ NMR by integration of peaks at 5.40 ppm ($J_1$=2.9 Hz) and 5.37 ppm ($J_1$=3.0 Hz) and was found to be 1 : 25 *syn* : *anti*.

The crude product was purified by FCC ($SiO_2$, hexane : ethyl acetate 97 : 3) to afford the TIPS-protected products **63g** (79 mg, 0.19 mmol) as yellow liquid in 58 % yield.

**63g**

**$[\alpha]^{22}_{D}$** -42 (c 0.92, chloroform)

**$[\alpha]^{22}_{D}$** -28 (c 1.35, benzene)

**$R_f$** 0.71 (dichloromethane : methanol 49 : 1)

**IR** (KBr): 2963, 2869, 1745, 1596, 1485, 1464, 1392, 1376, 1364, 1344, 1243, 1149, 1013, 920, 884, 823, 809 $cm^{-1}$

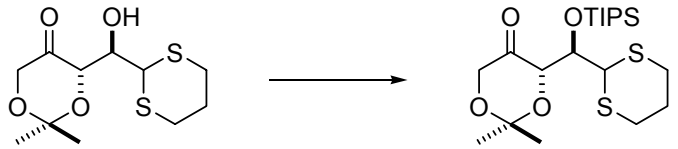
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:*7.27 (br s, 1H), 6.34 (d, $J_1$=3.1 Hz, 1H), 6.28 (dd, $J_1$=1.8 Hz, $J_2$=3.1 Hz, 1H), 5.37 (d, *J*=3.0 Hz, 1H), 4.53 (d, *J*=1.9 Hz, 1H), 4.18 (d, *J*=17.3 Hz, 1H), 4.05 (d, *J*=17.3 Hz, 1H), 1.34 (s, 3H), 1.03 (m, 3H), 1.02 (d, *J*=12.0 Hz, 12H), 1.01 (d, *J*=12.0 Hz, 6H), 0.92 (s, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.0, 153.7, 141.4, 110.5, 108.3, 104.0, 80.3, 69.9, 40.5, 25.2, 18.1, 16.5, 12.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 442 ($[M+18]^+$, 5), 381 (8), 268 (8), 253 (100), 193 (30), 185 (26), 96 (38)

**HRMS** *m/z* calcd for $C_{23}H_{40}O_5Si$ 442.2989 ($M+NH_4$), found 442.2996 (CI)

**4-(*S*)-4-[(*S*)-1-(triisopropylsilyloxy)-2-(1,3-dithian-2-yl)]-2,2-dimethyl-1,3-dioxan-5-one (51c)**




**7c** **51c**

*Reaction was done based on modified procedure S1*

To a cold solution of **7c** (0.35 g, 1.3 mmol, 1.0 eq) in dry THF (5.2 mL) were added dropwise 2,6-lutidine (0.27 g, 0.29 mL, 2.5 mmol, 2.0 eq) followed by TIPSOTf (0.46 g, 0.41 mL, 1.5 mmol, 1.2 eq). The reaction was stirred at -78 °C until no starting material was detected by TLC (1.5 h). Then saturated solution of $NaHCO_3$ was added, extracted with $CH_2Cl_2$ (x 3) and the combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FCC ($SiO_2$, hexane: ethyl acetate 95: 5) to afford **51c** (0.52 g, 1.2 mmol) as a white solid in 95 % yield.

**IR** (KBr): 2966, 2866, 1711, 1465, 1380, 1260, 1105, 1014, 882, 798 $cm^{-1}$

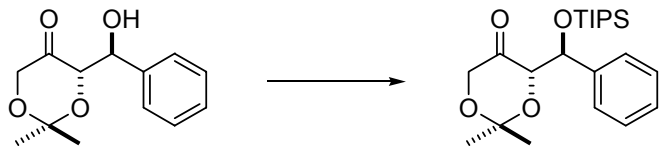
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.83 (d, *J*=9.6 Hz, 1H), 4.52 (dd, $J_1$=1.3 Hz, $J_2$=15.9 Hz, 1H), 4.47 (d, *J*=1.3 Hz, 1H), 3.89 (d, *J*=15.9 Hz, 1H), 3.80 (d, *J*=9.6 Hz, 1H), 2.85-2.79 (m, 1H), 2.55-2.46 (m, 2H), 2.35-2.28 (m, 1H), 1.99-1.92 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.16-1.10 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 204.7, 100.7, 79.3, 74.5, 67.3, 44.4, 26.3, 25.6, 25.1, 24.9, 23.4, 18.5, 17.9, 13.2

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 435 ($[M+1]^+$, 100), 377 (8), 305 (5), 261 (11), 148 (10), 119 (25)

**HRMS** *m/z* calcd for $C_{20}H_{38}O_4S_2Si$ 435.2059 (M+H), found 435.2066 (CI)

**4-(*S*)-4-[(*S*)-1-(triisopropylsilyloxy)-2-phenyl]-2,2-dimethyl-1,3-dioxan-5-one (51e)**




**7e** **51e**

*Reaction was done according to the procedure S1*

To the stirred solution (0 °C) of **7e** (34 mg, 0.14 mmol, 1.0 eq) in dry THF (1.3 mL) were added dropwise 2,6-lutidine (31 mg, 0.040 mL, 0.28 mmol, 2.0 eq) followed by TIPSOTf (53 mg, 0.050 mL, 0.17 mmol, 1.2 eq). The reaction was stirred at 0 °C until no starting material was detected by TLC. Then saturated solution of $NaHCO_3$ was added, extracted with $CH_2Cl_2$ (x 3) and the combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by FCC ($SiO_2$, hexane: ethyl acetate 97: 7) to afford **51e** (46 mg, 0.12 mmol) as a yellow oil in 82 % yield.

**$[\alpha]^{26}_D$** -44 (c 2.3, chloroform)

**$R_f$** 0.44 (hexane : ethyl acetate 9 : 1)

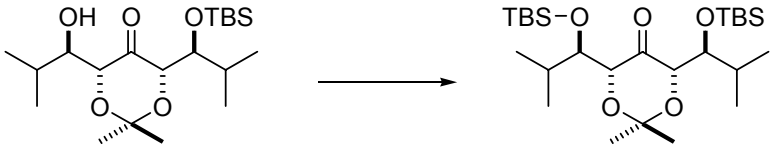
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.37-7.18 (m, 5H), 5.28 (d, *J*=2.9 Hz, 1H), 4.51 (dd, $J_1$=1.5 Hz, $J_2$=2.9 Hz, 1H), 3.91 (dd, $J_1$=1.5 Hz, $J_2$=16.3 Hz, 1H), 3.79 (d, *J*=16.3 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.09-1.01 (m, 3H), 1.00-0.93 (m, 18H),

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.4, 140.3, 128.2, 127.7, 127.6, 100.8, 80.2, 74.1, 67.4, 24.6, 23.5, 18.2, 18.1, 12.5

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 410($[M+ NH_4]^+$, 2), 349 (6), 291 (3), 263 (100), 219 (13), 185 (18), 174 (5)

**HRMS** *m/z* calcd for $C_{22}H_{36}O_4Si$ 410.2727 ($M+NH_4$), found 410.2727 (CI)

**(4S,6R)-6-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl]-4-[(*S*)-1-(*tert*-butyldimethylsilyloxy)-2-methylpropyl]-2,2-dimethyl-1,3-dioxan-5-one (60)**




**58** **60**

*Reaction was done based on the modified procedure S2*

To a cold solution of **58** (25 mg, 0.060 mmol, 1.0 eq) in dry THF (1 mL) were added dropwise 2,6-lutidine (14 mg, 15 μL, 0.13 mmol, 2.0 eq) followed by TBDMSOTf (21 mg, 19 μL, 0.080 mmol, 1.2 eq). The reaction was stirred at -78 °C until no starting material was detected by TLC (1 h). Then saturated solution of $NaHCO_3$ was added, extracted with $CH_2Cl_2$ (x 3) and the combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by SCC ($SiO_2$, hexane : ethyl acetate 97 : 3) to afford compound **60** (32 mg, 0.060 mmol) as a colorless liquid in 97 % yield.

**$[\alpha]^{26}_D$** -0.8 (c 1, chloroform)

**Rf** 0.66 (hexane : ethyl acetate 9 : 1)

**IR** (KBr): 2956, 2929, 2858, 1747, 1472, 1381, 1251, 1068, 1006, 837, 775, 666 $cm^{-1}$

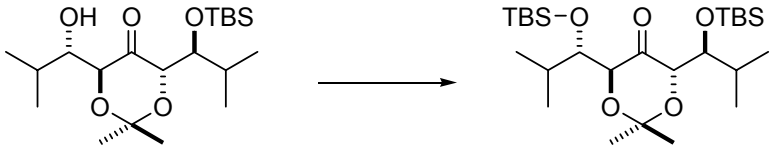
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.26 (d, *J*=3.2 Hz, 2H), 3.90 (dd, $J_1$=3.2 Hz, $J_2$=5.35 Hz, 2H), 2.01-1.93 (m, 2H), 1.51 (s, 3H), 1.50 (s, 3H), 0.92 (d, *J*=6.7 Hz, 6H), 0.87 (s, 18H), 0.84 (d, *J*=6.7 Hz, 6H), 0.06 (s, 12H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 204.9, 98.8, 81.1, 76.8, 30.9, 29.2, 26.3, 20.9, 19.8, 18.6, 1.2, -3.7, -4.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 503 ($[M+1]^+$, 100), 373 (23), 187 (96), 148 (67),132 (91)

**HRMS** *m/z* calcd for $C_{26}H_{54}O_5Si_2$ 503.3588 (M+H), found 503.3585 (CI)

**(4S,6S)-4,6-bis[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl]-2,2-dimethyl-1,3-dioxan-5-one (59)**




**57** **59**

*Reaction was done based on the modified procedure S2*

To a cold solution of **57** (19 mg, 0.050 mmol, 1.0 eq) in dry THF (1 mL) were added dropwise 2,6-lutidine (11 mg, 15 μL, 0.10 mmol, 2.0 eq) followed by TBDMSOTf (16 mg, 14 μL, 0.060 mmol, 1.2 eq). The reaction was stirred at -78 °C until no starting material was detected by TLC (1 h). Then saturated solution of $NaHCO_3$ was added, extracted with $CH_2Cl_2$ (x 3) and the combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by SCC ($SiO_2$, hexane : ethyl acetate 97 : 3) to afford compound **59** (19 mg, 0.040 mmol) as a colorless liquid in 78 % yield.

**$[\alpha]^{25}_D$** -104 (c 0.7, chloroform)

**Rf** 0.71 (hexane : ethyl acetate 9 : 1)

**IR** (KBr): 2956, 2931, 2858, 1728, 1472, 1383, 1257, 1122, 1068, 836, 777, 670 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.19 (d, *J*=3.1 Hz, 2H), 3.77 (dd, $J_1$=3.1 Hz, $J_2$=6.4 Hz, 2H), 2.04-1.95 (m, 2H), 1.41 (s, 6H), 0.90 (d, *J*=6.7 Hz, 6H), 0.86 (s, 18H), 0.83 (d, *J*=6.7 Hz, 6H), 0.06 (s, 12H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.7, 101.5, 76.5, 30.7, 26.3, 24.2, 20.0, 19.1, 18.5, 1.2, -3.8, -4.4

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 503 ($[M+1]^+$, 8), 371 (15), 299 (27), 257 (31), 234 (24), 187 (100), 132 (70)

**HRMS** *m/z* calcd for $C_{26}H_{54}O_5Si_2$ 503.3588 (M+H), found 503.3588 (CI)

### 3.7 The second aldol reaction

**General experimental procedure for aldol reaction of protected β-hydroxydioxanone**

Method L1: Formation of lithium enolate of dioxanone aldol followed by the reaction with aldehyde

A solution of *n*-BuLi in hexanes (2.5 M) or cyclohexanes (2.0 M; 1.0 - 4.3 eq, was added dropwise to the stirred solution of DIA (1.2-5.2 eq) in dry THF at 0 °C under nitrogen. After 30 min a solution of a dioxanone mono-aldol (1.0 eq) in THF was added slowly and the mixture was stirred at -78 °C for 0.5 - 2 h. The aldehyde (1.3 - 5.5 eq) was then added and, after 20 min, the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated to give the crude product. The crude product was fractionated by FCC (hexane : ethyl acetate 0-30 %) to provide the double aldol products.

**General experimental procedure for aldol reaction of protected β-hydroxydioxanone via boron enolate**

*(This procedure was adapted from Nowak's thesis.[7] The amounts of reagent were modified.)*

Method B1: Formation of boron enolate of dioxanone aldol in dichloromethane followed by the reaction with aldehyde

Triethylamine (2.0 - 10 eq) was dissolved in $CH_2Cl_2$ and the solution was cooled to 0 °C. Dicyclohexylboron chloride (1.0 M solution in hexane, 1.0-5.0 eq) was added, and the solution was stirred for 15 min. Next, the ketone (1.0 eq) was added as a solution in $CH_2Cl_2$ and, after stirring for 15 min, the aldehyde (1.1 - 5.5 eq) was added. After

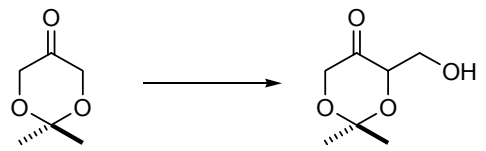
stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to 0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1H$ NMR or $^{13}C$ NMR on the crude product. The products was isolated by FCC (hexane : ethyl acetate) to provide pure bis aldol products.

*(This procedure was adapted from ref.[11] The amounts of reagent were modified.)*

Method B2: Formation of boron enolate of dioxanone aldol in diethyl ether followed by the reaction with aldehyde

Triethylamine (2.0 - 10 eq) was dissolved in ether and the solution was cooled to -78 °C. Dicyclohexylboron chloride (1.0 M solution in hexane, 1.0 - 5.0 eq) was added, and the solution was stirred for 30 min. Next, the ketone (1.0 eq) was added as a solution in $CH_2Cl_2$ and, after stirring for 30 min, the aldehyde (1.1 - 5.5 eq) was added. After stirring for 30 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to 0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1H$ NMR or $^{13}C$ NMR on the crude product. The products was isolated by FCC (hexane : ethyl acetate) to provide pure bis aldol products.

**(rac)-4-Hydroxymethyl-2,2-dimethyl-1,3-dioxan-5-one (3)**




**1a** **3**

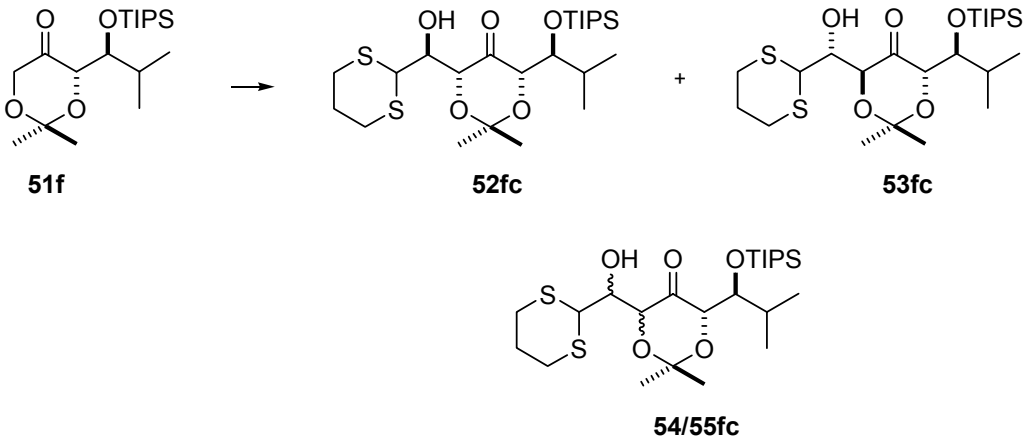
*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.22 mL, 0.55 mmol, 2.5 M solution in hexanes, 1.1 eq) was added dropwise to a stirred solution of DIA (0.11 mL, 0.60 mmol, 1.2 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution of **1a** (65 mg, 0.50 mmol, 1.0 eq) was added slowly and the mixture was stirred for 1 h at -78 °C. Formaldehyde (approx. 40 eq; gas) was then added. After 20 min the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$ and concentrated to give the crude product. The crude product was fractionated by column chromatography (10 % ethyl acetate in hexane) to give **3** (10 mg, 12 %). Due to the instability of the product it was only partially characterized.

**IR** (KBr): 3402, 2958, 2922, 1729, 1261, 1094, 1019, 800 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.33 (ddd, $J_1$=1.5 Hz, $J_2$=5.1 Hz, $J_3$=6.4 Hz, 1H), 4.26 (dd, $J_1$=1.5 Hz, $J_2$=17.1 Hz, 1H), 4.02 (d, $J$=17.1 Hz, 1H), 3.91-3.87 (m, 2H), 2.07-2.02 (m, 1H), 1.48 (s, 3H), 1.46 (s, 3H)

**Compound 52fc and 53fc**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.28 mL, 0.64 mmol, 2.3 M solution in hexanes, 4.3 eq) was added dropwise to a stirred solution of DIA (0.12 mL, 0.70 mmol, 4.7 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution of **51f** (53 mg, 0.15 mmol, 1.0 eq) was added slowly and the mixture was stirred for 2 h at -78 °C. Aldehyde **2c** (109 mg, 0.74 mmol, 5.0 eq) was added fast and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude product. The diastereoselectivity of the reaction was determined by $^1$H NMR on the crude product by integration of the peaks at 1.56 ppm and 1.49 ppm and was found to be 87 : 13 : 01 of **52 : 53 : 54/55**. The crude product was fractionated by FCC (5 % ethyl acetate in hexanes) to give **52fc** (40 mg, 58 %, BORSM 64 %), **53fc** (6.0 mg, 9 %, BORSM 10 %) and **54/55fc** (5.0 mg, 7 %). Only major product was fully characterized.

**52fc**

**$[\alpha]^{24}_D$** +10 (c 1, chloroform)

**$[\alpha]^{25}_D$** +10 (c 1, benzene)

**mp** 105-107 °C

**$R_f$** 0.71 (hexane : ethyl acetate 9 : 1)

**IR** (KBr): 3490, 1708 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.52 (dd, $J_1$=1.0 Hz, $J_2$=7.0 Hz, 1H), 4.44 (dd, $J_1$=1.0 Hz, $J_2$=2.1 Hz, 1H), 4.33 (dd, $J_1$=4.0 Hz, $J_2$=7.0 Hz, 1H), 4.20 (dd, $J_1$=2.1 Hz, $J_2$=6.1 Hz, 1H), 4.06 (d, $J$=4.0 Hz, 1H) 3.71 (br s, 1H), 3.14-3.11 (m, 2H), 2.67-2.64 (m, 1H), 2.60-2.58 (m, 1H), 2.04-2.00 (m, 2H), 1.98-1.89 (m, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.06 (m, 21H), 0.99 (d, $J$=6.9 Hz, 3H), 0.82 (d, $J$=6.9 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 208.9, 99.1, 82.0, 77.5, 77.3, 75.9, 44.2, 31.7, 29.0, 28.0, 27.6, 25.7, 20.6, 19.8, 19.1, 18.4, 18.3, 13.1

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 507 ($[M+1]^+$, 68), 359 (12), 229 (100), 209 (12), 202 (11), 174 (19), 119 (42)

**HRMS** *m/z* calcd for $C_{24}H_{46}O_5S_2Si$ 507.2634 (M+H), found 507.2629 (CI)

**Anal.** Calcd for $C_{24}H_{46}O_5S_2Si$ C 56.87, H 9.15. Found: C 56.74, H 8.89

**53fc**

**IR:** 3438, 1733 $cm^{-1}$

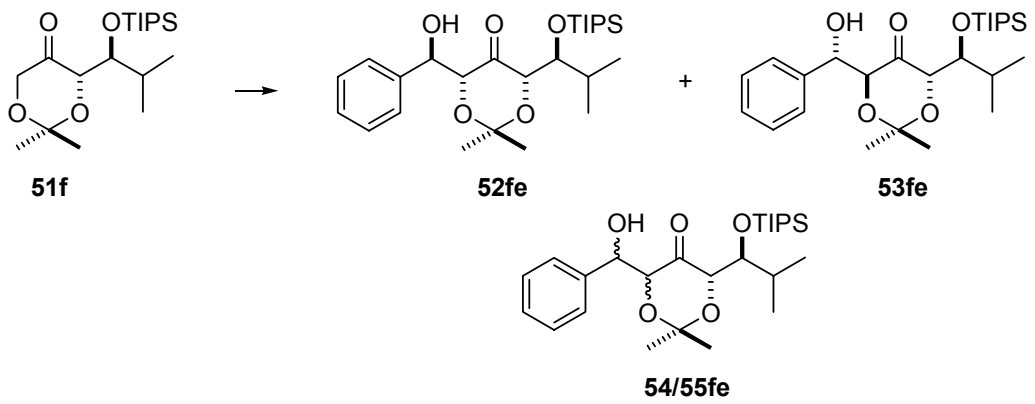
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.53-4.45 (m, 2H), 4.51 (d, $J$=1.8 Hz, 1H), 4.07 (dd, $J_1$=1.8 Hz, $J_2$=6.7 Hz, 1H), 3.87 (d, $J$=6.4 Hz, 1H), 3.16 (br s, 1H) 3.07-3.00 (m, 1H), 2.96-2.89 (m, 1H), 2.58-2.52 (m, 1H), 2.51-2.45 (m, 1H), 2.08-1.92 (m, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.12-1.02 (m, 21H), 0.96 (d, $J$=6.9 Hz, 3H), 0.85 (d, $J$=6.9 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 209.3, 101.8, 78.5, 77.1, 74.6, 73.3, 44.0, 27.1, 26.2, 25.5, 24.4, 24.1, 20.0, 19.7, 18.6, 18.5, 13.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 507 ($[M+1]^+$, 42), 359 (18), 229 (100), 202 (9), 174 (15), 119 (26)

**HRMS** *m/z* calcd for $C_{24}H_{46}O_5S_2Si$ 507.2634 (M+H), found 507.2623 (CI)

**Compound 52fe and 53fe**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.24 mL, 0.46 mmol, 1.9 M solution in cyclohexanes, 3.7 eq) was added dropwise to a stirred solution of DIA (0.090 mL, 0.50 mmol, 4.0 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution of **51f** (45 mg, 0.12 mmol, 1.0 eq) was added slowly and the mixture was stirred for 2 h at -78 °C. Benzaldehyde (104 mg, 0.10 mL, 1.0 mmol, 8.0 eq) was added fast and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude products. The diastereoisomer ratio was determined by $^1H$ NMR by integration of peaks at 4.95 ppm ($J$=6.8 Hz), 4.81 ppm ($J$=8.2 Hz) 5.19 ppm ($J$=1.3 Hz) and was found to be **52fe : 53fe : 54/55fe** in ratio 76 : 14 : 10. The crude product was fractionated by chromatography column using silica gel (3 - 5 % ethyl acetate in hexane) to give **54/55fe** (3.0 mg, 5 %), **53fe** (5.0 mg, 9 %) and **52fe** (50 mg, 86 %).

**52fe**

**$[\alpha]^{24}_D$** +130 (c 1.39, benzene)

**IR** (KBr): 3482, 2958, 2943, 2867, 1721, 1464, 1384, 1203, 1164, 1149, 1081, 1065, 883, 698 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.37-7.26 (m, 5H), 4.95 (d, $J$=6.8 Hz, 1H), 4.43 (d, $J$=2.0 Hz, 1H), 4.37 (d, $J$=6.8 Hz, 1H), 4.15 (dd, $J_1$=2.0 Hz, $J_2$=5.7 Hz, 1H), 3.67 (br s, 1H), 1.61-1.57 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.12-1.09 (m, 21H), 0.91 (d, $J$=6.6 Hz, 3H), 0.71 (d, $J$=6.6 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 208.2, 139.4, 128.2, 128.1, 127.9, 98.9, 82.1, 79.2, 77.4, 74.3, 31.7, 28.9, 20.7, 19.9, 18.9, 18.4, 18.3, 13.1

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 482 ($[M+18]^+$, 92), 476 (58), 465 ($[M+1]^+$, 100)

**HRMS** *m/z* calcd for $C_{26}H_{44}O_5Si$ 465.3036 (M+H), found 465.3047 (CI)

**53fe**

**IR** (KBr): 3526, 2939, 2867, 1744, 1464, 1387, 1224, 1094, 1012, 883, 680 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.40-7.26 (m, 5H), 4.81 (d, $J$=8.2 Hz, 1H), 4.35(dd, $J_1$=1.5 Hz, $J_2$=1.9 Hz, 1H), 4.23 (dd, $J_1$=1.3 Hz, $J_2$=8.2 Hz, 1H), 4.07 (dd, $J_1$=1.9 Hz, $J_2$=6.6 Hz, 1H), 3.66 (br s, 1H), 2.01-1.94 (ddd, $J_1$=6.6 Hz, $J_2$=6.9 Hz, $J_3$=6.9 Hz, 1H), 1.33 (s, 3H), 1.19 (s, 3H), 1.14-1.01 (m, 21H), 0.96 (d, $J$=6.9 Hz, 3H), 0.87 (d, $J$=6.9 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 211.8, 139.8, 128.2, 128.1, 127.3, 101.8, 79.3, 77.7, 75.8, 72.9, 32.1, 23.8, 20.0, 19.6, 18.5, 18.4, 18.3, 13.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 482 ($[M+18]^+$, 41), 465 ($[M+1]^+$, 34), 359 (23), 229 (100), 174 (24), 77 (2)

**HRMS** *m/z* calcd for $C_{26}H_{44}O_5Si$ 465.3036 (M+H), found 465.3048 (CI)

**54/55fe**

**IR** (KBr): 3436, 2940, 2867, 1724, 1463, 1385, 1241, 1092, 1062, 883, 679 $cm^{-1}$

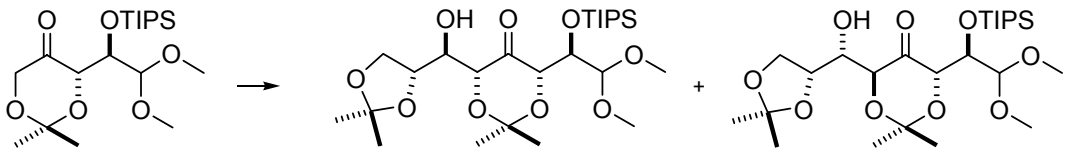
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.42-7.25 (m, 5H), 5.19 (dd, $J_1$=1.3 Hz, $J_2$=7.2 Hz, 1H), 4.39 (dd, $J_1$=1.3 Hz, $J_2$=3.1 Hz, 1H), 4.32 (dd, $J_1$=1.3 Hz, $J_2$=2.4 Hz, 1H), 4.07 (dd, $J_1$=2.4 Hz, $J_2$=6.4 Hz, 1H), 2.72 (d, $J$=7.2 Hz, 1H), 2.00-1.92 (m, 1H), 1.46 (s, 3H), 1.33 (s, 3H), 1.14-0.99 (m, 21H), 0.94 (d, $J$=6.8 Hz, 3H), 0.84 (d, $J$=6.8 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.8, 140.5, 128.5, 128.0, 126.8, 101.9, 79.2, 77.5, 77.1, 71.2, 32.0, 24.3, 24.1, 19.9, 19.4, 18.5, 18.4, 13.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 465 ($[M+1]^+$, 17), 391 (6), 359 (29), 257 (10), 229 (100), 174 (18)

**HRMS** *m/z* calcd for $C_{26}H_{44}O_5Si$ 465.3036 (M+H), found 465.3035 (CI)

**Bis aldols 52hd and 53hd**




**51h** **52hd** **53hd**

*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.25 mL, 0.49 mmol, 1.9 M solution in cyclohexane, 3.7 eq) was added dropwise to a stirred solution of DIA (0.090 mL, 0.50 mmol, 3.8 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution of **51h** (51 mg, 0.13 mmol, 1.0 eq) was added slowly and the mixture was stirred for 2 h at -78 °C. Aldehyde (65 mg, 0.50 mmol, 3.8 eq) was added fast and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude products. The crude product was fractionated by FCC (3 – 5 % ethyl acetate in hexane) to give **53hd** (8.2 mg, 0.020 mmol, 12 % yield, BORSM 21 %), **52hd** (22 mg, 0.040 mmol, 33 % yield, BORSM 58 %) and recovered **51h** (22 mg). Only partial data is reported.

*Reaction was done based on the modified procedure B1*

Triethylamine (0.36 mL, 2.6 mmol, 6.0 eq) was dissolved in $CH_2Cl_2$ (10 mL) and the solution was cooled to 0 °C. Dicyclohexylboron chloride (1.3 mL, 1.3 mmol, 3.0 eq, 1.0 M solution in hexane) was added, and the solution was stirred for 15 min. Next, ketone **51h** (156 mg, 0.40 mmol, 1.0 eq) was added as a solution in $CH_2Cl_2$, and, after stirring for 15 min, (*R*)-glyceraldehyde (338 mg, 2.6 mmol, 6.0 eq) was added. After stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to

0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1$H NMR on the crude product by integration of the peaks at 4.53 (d, *J*=7.2 Hz) and 4.49 (d, *J*=7.3 Hz) and was found to 11 : 89 of **52hd** to **53hd**. The products was isolated by FCC (5 % ethyl acetate in hexane) to give **53hd** (146 mg, 0.28 mmol, 70 %) and **52hd** (17 mg, 0.032 mmol, 8 %).

**52hd:**

**IR** (KBr): 3439, 2932, 2857, 1737, 1461, 1380, 1254, 1204, 1072, 837, 780 $cm^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) $\delta$: 4.53 (d, *J*=7.5 Hz, 1H), 4.36 (s, 1H), 4.32 (d, *J*=7.5 Hz, 1H), 4.25 (m, 1H), 4.24 (s, 1H), 4.22 (d, *J*=8.0 Hz, 1H), 3.99 (dd, $J_1$=7.8 Hz, $J_2$=7.8 Hz, 1H), 3.89 (dd, $J_1$=7.8 Hz, $J_2$=7.8 Hz, 1H), 3.82 (dd, $J_1$=5.0 Hz, $J_2$=8.0 Hz, 1H), 3.46 (s, 3H), 3.35 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.07 (m, 21H)

$^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 4.53 (d, *J*=7.2 Hz, 1H), 4.42-4.34 (m, 4H), 4.03-3.98 (m, 3H), 3.40 (s, 3H), 3.33 (s, 3H), 3.07 (d, *J*=4.4 Hz, 1H), 1.53 (s, 6H), 1.40 (s, 3H), 1.34 (s, 3H), 1.10-1.0 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *$\delta$:* 204.9, 109.2, 105.4, 98.9, 80.5, 76.2, 73.2, 72.5, 65.9, 55.8, 55.2, 29.0. 26.8, 25.6, 20.3, 18.2, 12.8

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 538 ($[M+18]^+$, 65), 506 (29), 489 (74),474 (42), 448 (25), 408 (21), 376 (100), 359 (58), 344 (21), 185 (22), 148 (26), 131 (39), 75 (39)

**HRMS** *m/z* calcd for $C_{25}H_{48}O_9Si$ 505.2833 (M - $CH_3$), found 505.2829 (EI)

**53hd**

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.49 (d, *J*=7.3 Hz, 1H), 4.32 (d, *J*=1.5 Hz, 1H), 4.29 (dd, $J_1$=1.5 Hz, $J_2$=7.3 Hz, 1H), 4.22 (dd, $J_1$=5.0 Hz, $J_2$=6.7 Hz, $J_3$=7.9 Hz, 1H), 4.19 (d, *J*=8.3 Hz, 1H), 3.96 (dd, $J_1$=6.7 Hz, $J_2$=7.9 Hz, 1H), 3.85 (dd, $J_1$=7.6 Hz, $J_2$=7.9 Hz,

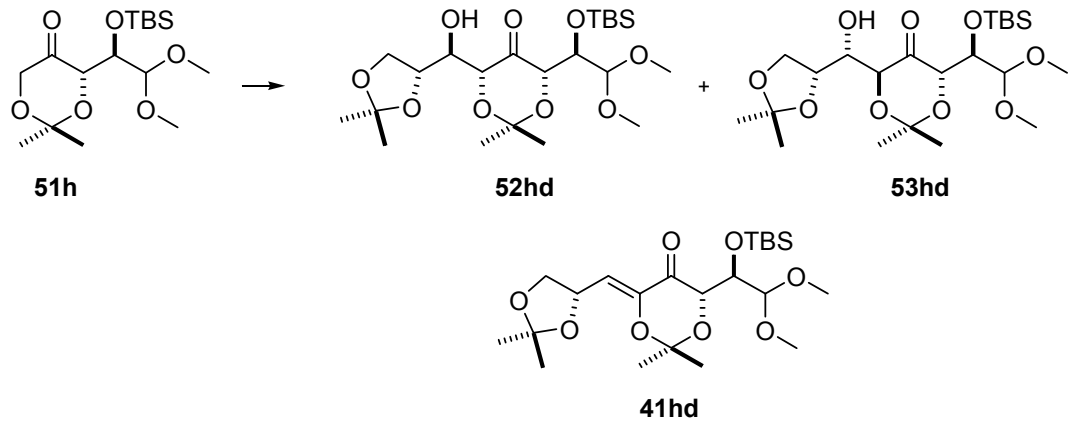
1H), 3.79 (dd, $J_1$=5.0 Hz, $J_2$=8.3 Hz, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 3.13 (br s, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.15-1.00 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.0, 109.2, 105.5, 101.9, 78.7, 75.8, 73.8, 72.1, 70.1, 66.0, 56.1, 55.5, 26.5, 25.9, 24.4, 23.8, 18.3, 18.2, 12.8

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 538 ($[M+18]^+$, 65), 506 (29), 489 (74),474 (42), 448 (25), 408 (21), 376 (100), 359 (58), 344 (21), 185 (22), 148 (26), 131 (39), 75 (39)

**HRMS** *m/z* calcd for $C_{25}H_{48}O_9Si$ 538.3411 ($M+NH_4$), found 538.3430 (CI)

**Bis aldols 52hd and 53hd**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.79 mL, 1.9 mmol, 2.4 M solution in hexanes, 3.3 eq) was added dropwise to a stirred solution of DIA (0.36 mL, 2.1 mmol, 3.6 eq) in THF (10 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **51h** (200 mg, 0.57 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 2 h at -78 °C. Freshly prepared (*R*)-glyceraldehyde was added (448 mg, 3.4 mmol, 6.0 eq) then and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 5 mL) and extracted with ether (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated, and fractionated by FCC (hexanes : ethyl acetate 3 - 20%) to give the recovered staring material **51h** (20 mg, 10 %), α β-unsaturated ketone **41hd** (42 mg, 16 %) as a colorless oil, **53hd** (53 mg, 0.11 mmol, 19 %, BORSM 22 %) as a colorless oil and **52hd** (156 mg, 0.33 mmol, 57 %, BORSM 63 %) as pale yellow liquid. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at δ 3.48 ppm and 3.36 ppm and was found to be 14 : 86 of *anti-trans-anti* to *anti-cis-anti* aldols.

The reaction was repeated several times and, generally preceded with diastereoselectivity from 14 : 86 to 12 : 88 of **53** to **52** and in 76 -94 % combined yield.

**52hd**

**$[\alpha]^{23}_{D}$** -6 (c 1.2, chloroform)

**IR** (KBr): 3449, 1737 $cm^{-1}$

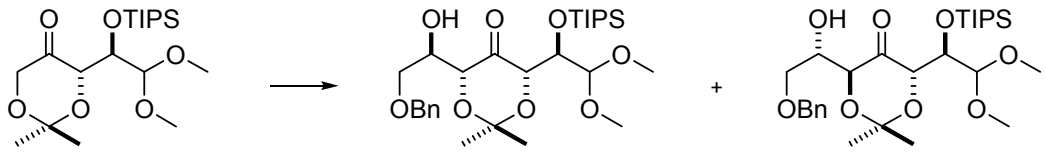
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.57 (d, *J*=7.4 Hz, 1H), 4.38 (dd, $J_1$=1.0 Hz, $J_2$=1.8 Hz, 1H), 4.35 (dd, $J_1$=1.0 Hz, $J_2$=4.7 Hz, 1H), 4.32 (ddd, $J_1$=1.0 Hz, $J_2$=1.0 Hz, $J_3$=7.3 Hz, 1H), 4.07 (dd, $J_1$=1.8 Hz, $J_2$=7.4 Hz, 1H), 4.06 (ddd, $J_1$=3.9 Hz, $J_2$=4.7 Hz, $J_3$=7.3 Hz, 1H), 4.02 (dd, $J_1$=1.0 Hz, $J_2$=6.4 Hz, 2H), 3.42 (s, 3H), 3.36 (s, 3H), 2.89 (d, *J*=3.9 Hz, 1H), 1.52 (s, 6H), 1.40 (s, 3H), 1.34 (s, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 205.4, 109.1, 105.4, 99.0, 79.8, 78.1, 76.1, 74.1, 72.4, 65.8, 56.3, 55.4, 29.0, 26.8, 26.1, 26.0, 25.6, 20.6, 18.4, -4.3, -4.4

**LRMS** (CI), *m/z* (relative intensity): 496 ($[M+18]^+$, 100), 464 (40), 352 (24), 320 (20), 219 (14), 75 (13)

**HRMS** *m/z* calcd for $C_{22}H_{42}O_9Si$ 496.2942 ($M+NH_4$), found 496.2954 (CI)

**Bis aldol 52hb**




**51h** **52hb** **53hb**

*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.19 mL, 0.37 mmol, 1.9 M solution in cyclohexane, 3.0 eq) was added dropwise to a stirred solution of DIA (0.070 mL, 0.41 mmol, 3.3 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution of **51h** (52 mg, 0.13 mmol, 1.0 eq) was added slowly and the mixture was stirred for 30 min at -78 °C. Aldehyde (59 mg, 0.39 mmol, 3.0 eq) was added fast and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude products. The diastereoisomer ratio was determined by $^1$H NMR by integration of peaks at 1.51 ppm and 1.40 ppm and was found to be 56 : 44 of **52hb** : **53hb**. The crude product was fractionated by chromatography column using silica gel (3 - 5 % ethyl acetate in hexane) The crude product was fractionated by chromatography column (5 - 10 % ethyl acetate in hexane) to give both isomeric products (51 mg, 9.5 $10^{-3}$ mmol, 71 %) as a colorless oil. Further purification provided partial separation and characterization of major component of this mixture, which was fully characterized.

**52hb**

$[\alpha]^{22}_D$ +2 (c 0.7, benzene)

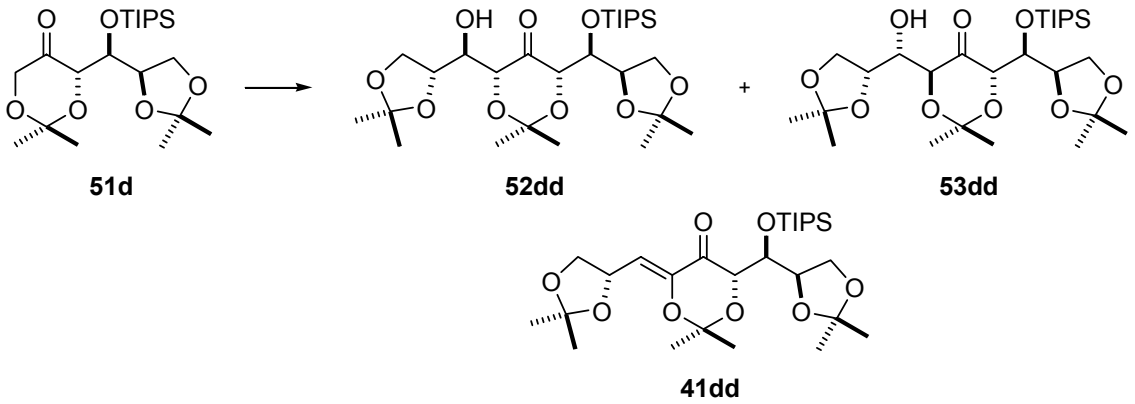
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.47-7.24 (m, 5H), 4.65 (d, $J$=12.0 Hz, 1H), 4.51 (d, $J$=12.0 Hz, 1H), 4.50 (d, $J$=7.2 Hz, 1H), 4.39 (d, $J$=1.0 Hz, 1H), 4.37 (dd, $J_1$=1.0 Hz, $J_2$=7.4 Hz, 1H), 4.31 (d, $J$=8.0 Hz, 1H), 4.09 (m, 1H), 3.64 (m, 2H), 3.64 (br s, 1H), 3.41 (s, 3H), 3.32 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H), 1.11-1.01 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.6, 138.6, 128.5, 127.9, 127.7, 105.8, 98.7, 80.4, 75.5, 73.8, 73.6, 71.6, 69.7, 55.8, 55.7, 29.0, 20.3, 18.2, 12.8

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 558 ($[M+18]^+$, 1), 491 (10), 359 (47), 168 (100)

**HRMS** *m/z* calcd for $C_{28}H_{48}O_8Si$ 558.3462 ($M+NH_4$), found 558.3474 (CI)

**Bis aldols 52dd and 53dd**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.25 mL, 0.49 mmol, 1.9 M solution in cyclohexane, 3.7 eq) was added dropwise to a stirred solution of DIA (0.090 mL, 0.50 mmol, 3.8 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution of **51d** (55 mg, 0.13 mmol, 1.0 eq) was added slowly and the mixture was stirred for 2 h at -78 °C. Aldehyde (65 mg, 0.50 mmol, 3.8 eq) was added fast and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7; 5 mL) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude products in 59 : 49 ratio of **52dd** : **53dd**. The crude product was fractionated by FCC (3-10 % ethyl acetate in hexane) to give recovered starting material **51d** (10 mg, 18 %), **53dd** (23 mg, 0.040 mmol, 34 %, BORSM 40 %), **52dd** (35 mg, 0.060 mmol, 49 %, BORSM 60 %) and traces of condensation product **41dd**. Only partial data is reported.

**52dd**

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.49 (dd, $J_1$=1.8 Hz, $J_2$=7.1 Hz, 1H), 4.36-4.30 (m, 2H), 4.26-4.20 (m, 2H), 4.39-3.85 (m, 4H), 4.78 (dd, $J_1$=4.6 Hz, $J_2$=8.1 Hz, 1H), 3.08 (br s, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.15-1.06 (m, 3H), 1.06-1.01 (m, 18H)

**53dd**

**$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$: 5.45 (dd, $J_1$=3.5 Hz, $J_2$=9.3 Hz, 1H), 4.80 (dd, $J_1$=1.0 Hz, $J_2$=9.3 Hz, 1H), 4.52 (ddd, $J_1$=3.5 Hz, $J_2$=5.2 Hz, $J_3$=6.8 Hz, 1H), 4.43 (dd, $J_1$=1.4 Hz, $J_2$=7.0 Hz, 1H), 4.28 (ddd, $J_1$=7.0 Hz, $J_2$=7.1 Hz, $J_3$=7.1 Hz, 1H), 4.20 (dd, $J_1$=1.0 Hz, $J_2$=1.4 Hz, 1H), 4.05 (dd, $J_1$=7.2 Hz, $J_2$=9.1 Hz, 1H), 3.94 (dd, $J_1$=7.1 Hz, $J_2$=7.9 Hz, 1H), 3.91 (dd, $J_1$=7.0 Hz, $J_2$=7.2 Hz, 1H), 3.79 (dd, $J_1$=5.2 Hz, $J_2$=9.1 Hz, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.41 (s, 6H), 1.32 (s, 3H), 1.26 (s, 3H), 1.11-1.02 (m, 3H), 1.03-0.97 (m, 18H), (OH group not present in the $^{1}$H NMR)

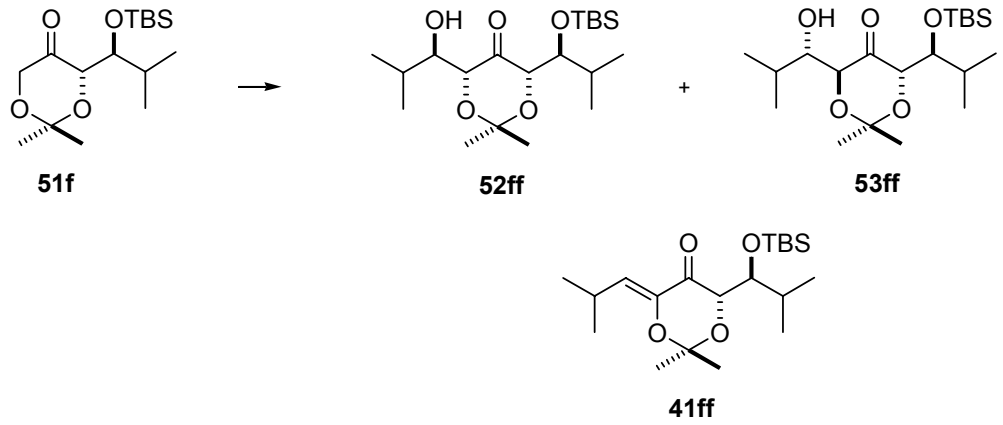
**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ: 205.5, 109.8, 109.7, 102.4, 78.8, 76.3, 74.0, 73.4, 72.1, 70.5, 66.5, 65.5, 26.7, 26.4, 25.2, 25.1, 24.4, 23.6, 18.3, 18.2, 12.6

**41dd**

**$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$: 5.94 (d, $J$=6.9 Hz, 1H), 4.81 (ddd, $J_1$=6.9 Hz, $J_2$=6.9 Hz, $J_3$=6.9 Hz, 1H), 4.49 (dd, $J_1$=1.4 Hz, $J_2$=7.2 Hz, 1H), 4.31 (ddd, $J_1$=7.2 Hz, $J_2$=8.0 Hz, $J_3$=8.0 Hz, 1H), 4.29 (d, $J$=1.6 Hz, 1H), 4.13 (dd, $J_1$=6.7 Hz, $J_2$=7.9 Hz, 1H), 3.96 (dd, $J_1$=7.5 Hz, $J_2$=7.5 Hz, 1H), 3.88 (dd, $J_1$=8.2 Hz, $J_2$=8.2 Hz, 1H), 3.56 (dd, $J_1$=7.8 Hz, $J_2$=7.8 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.15-1.06 (m, 3H), 1.06-0.89 (m, 18H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *$\delta$:* 190.1, 147.0, 115.7, 109.8, 109.5, 100.6, 79.4, 76.7, 74.8, 71.2, 69.2, 66.3, 28.1, 26.8, 26.2, 26.0, 25.4, 23.0, 18.2, 12.7

**Bis aldol 52ff and 53ff**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.22 mL, 0.56 mmol, 2.5 M solution in hexanes, 2.2 eq) was added dropwise to a stirred solution of DIA (61 mg, 0.090 mL, 0.61 mmol, 2.4 eq) in dry THF (5 mL) at 0 °C under nitrogen. After 30 min reaction mixture was cooled to -78 °C and after a few minutes a solution of compound **51f** (80 mg, 0.25 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 30 min at -78 °C. Isobutyraldehyde (49 mg, 0.68 mmol, 2.7 eq) was added and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7; 5 mL) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude product as a mixture **52ff** and **53ff** in 1.7 : 1 ratio (by $^{13}C$ NMR integrated at 98.90 and 101.48 ppm). The crude product was fractionated by PTLC (hexane : ethyl acetate 95 : 5 x 2) to give an α,β-unsaturated ketone **41ff** (2.2 mg, 0.020 mmol, 2.4 %) as a pale yellow liquid, the recovered starting material **51f** (11 mg, 0.14 mmol, 14 %), **53ff** (22 mg, 0.060 mmol, 24 % yield) as a colorless liquid and **52ff** (25 mg, 0.070 mmol, 27 %) as a colorless liquid.

**Major diastereoisomer 52ff**

$[\alpha]^{25}_{D}$ -4.94 (c 1.25, chloroform)

**Rf** 0.41 (hexane: ethyl acetate 9:1)

**IR** (KBr): 3552, 2959, 2932, 2858, 1735, 1472, 1382, 1252, 1219, 1170, 1070, 1005, 838, 775 $cm^{-1}$

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.35 (dd, $J_1$=1.1 Hz, $J_2$ =2.5 Hz, 1H), 4.03 (dd, $J_1$=1.1 Hz, $J_2$ =8.4 Hz, 1H), 3.80 (dd, $J_1$=2.5 Hz, $J_2$ =7.6 Hz, 1H), 3.76 (d, *J* =8.4 Hz, 1H), 3.26 (br s, 1H), 2.08-1.98 (m, 2H), 1.52 (s, 3H), 1.49 (s, 3H), 0.98 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.87 (s, 9H), 0.85 (d, *J*=7.0 Hz, 3H), 0.84 (d, *J*=6.7 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 210.8, 98.9, 80.6, 78.5, 77.4, 74.9, 31.1, 29.0, 28.2, 26.3, 20.7, 20.1, 19.6, 19.4, 18.5, 14.8, -3.6, -4.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 406 ($[M+18]^+$, 34), 389 ($[M+1]^+$, 4), 371 (3), 334 (3), 317 (21), 188 (16), 187 (100), 132 (33)

**HRMS** *m/z* calcd for $C_{20}H_{40}O_5Si$ 406.2889 ($M+NH_4$), found 406.2887 (CI)

**<u>Minor diastereoisomer 53ff</u>**

**$[\alpha]^{25}_{D}$** -110 (c 0.95, chloroform)

**Rf** 0.46 (hexane : ethyl acetate 9 : 1)

**IR** (KBr): 3558, 2959, 2932, 2858, 1715, 1472, 1382, 1252, 1219, 1170, 1070, 1006, 838 $cm^{-1}$

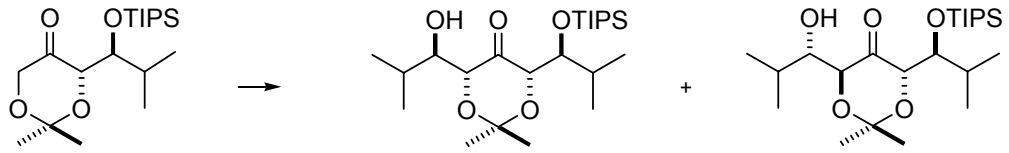
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.27 (dd, $J_1$=1.2 Hz, $J_2$ =2.0 Hz, 1H), 4.04 (dd, $J_1$=1.2 Hz, $J_2$ =8.4 Hz, 1H), 3.74 (dd, $J_1$=2.0 Hz, $J_2$ =7.9 Hz, 1H), 3.66 (dd, $J_1$=2.9 Hz, $J_2$=8.4 Hz, 1H), 3.02 (br s, 1H), 2.09-2.00 (m, 1H), 2.00-1.93 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 0.98 (d, *J*=7.0 Hz, 3H), 0.91 (d, *J*=6.7 Hz, 3H), 0.90-0.87 (m, 6H), 0.86 (s, 9H), 0.82 (d, *J*=7.0 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 212.7, 101.5, 78.2, 77.8, 74.1, 73.4, 31.0, 28.6, 26.2, 24.5, 23.8, 20.2, 19.8, 19.5, 18.4, 15.3, -3.8, -4.3

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 389 ($[M+1]^+$, 19), 371 (14), 334 (15), 317 (100), 299 (10), 259 (29), 241 (8)

**HRMS** *m/z* calcd for $C_{20}H_{40}O_5Si$ 389.2723 (M+H), found 389.2714 (CI)

**Bis aldol 52ff and 53ff**




**51f** **52ff** **53ff**

*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.26 mL, 0.6 mmol, 2.3 M solution in hexanes, 4.4 eq) was added dropwise to a stirred solution of DIA (0.11 mL, 0.66 mmol, 4.8 eq) in dry THF (5 mL) at 0 °C under nitrogen. After 30 min reaction mixture was cooled to -78 °C and after a few minutes a solution of **51f** (50 mg, 0.14 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 30 min at -78 °C. Isobutyraldehyde (49 mg, 0.68 mmol, 5.0 eq) was added and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7; 5 mL) and extracted with ether (x 3). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, concentrated to give the crude product as a mixture **52ff** and **53ff** in 1.9 : 1 ratio (by $^1$H NMR integrated at 1.54 ppm and 1.39 ppm). The crude product was fractionated by FCC (hexane : ethyl acetate 95 : 5) to give **52ff** (34 mg, 0.078 mmol, 57 % yield) as a colorless liquid and **53ff** (10 mg, 0.023 mmol, 17 %) as a colorless liquid.

*Reaction was done based on the modified procedure B2*

Triethylamine (43 mg, 0.060 mL, 0.42 mmol, 10 eq) was dissolved in $Et_2O$ (3 mL) and the solution was cooled to -78 °C. Dicyclohexylboron chloride (0.21 mL, 0.21 mmol, 5.0 eq, 1.0 M solution in hexane) was added, and the solution was stirred for 30 min. Next, the ketone **51f** (15 mg, 0.042 mmol, 1.0 eq) was added as a solution in $Et_2O$, and, after stirring for 30 min, isobutyraldehyde (30 mg, 0.42 mmol, 10 eq) was added. After stirring for 30 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried

with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to 0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1$H NMR on the crude product by integration of the peaks at 5.15 ppm and 4.42 ppm and 4.32 ppm and was found to be 1 : 13 : 86. The products was isolated by PTLC (hexane : ethyl acetate 4 :1) to provide a pure **53ff** (16 mg, 0.036 mmol, 86 %) and **52ff** (1.8 mg, 10 %). Only the major product was characterized.

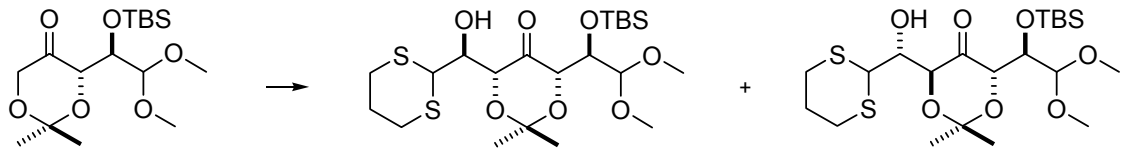
*Reaction was done based on the modified procedure B1*

Triethylamine (0.040 mL, 0.25 mmol, 6.0 eq) was dissolved in $CH_2Cl_2$ (2 mL) and the solution was cooled to 0 °C. Dicyclohexylboron chloride (0.13 mL, 0.13 mmol, 3.0 eq, 1.0 M solution in hexane) was added, and the solution was stirred for 15 min. Next, ketone **51f** (15 mg, 0.040 mmol, 1.0 eq) was added as a solution in $CH_2Cl_2$, and, after stirring for 15 min, isobutyraldehyde (18 mg, 0.25 mmol, 6.0 eq) was added. After stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to 0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1$H NMR on the crude product by integration of the peaks at 4.42 ppm and 4.32 ppm and was found to be 12 : 88 of adducts **52ff** and **53ff**. The products was isolated by PTLC (hexane : ethyl acetate 4 :1) to provide a pure **52ff** (13 mg, 3.0 $10^{-2}$ mmol, 71 %) and **53ff** (1.9 mg, 4.4 $10^{-3}$ mmol, 11 %). Only partial date is reported.

**53ff**

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.34 (dd, $J_1$=1.2 Hz, $J_2$ =2.0 Hz, 1H), 4.08 (dd, $J_1$=2.1 Hz, $J_2$ =6.7 Hz, 1H), 4.06 (dd, $J_1$=1.2 Hz, $J_2$ =8.6 Hz, 1H), 3.68 (ddd, $J_1$=2.7 Hz, $J_1$=2.9 Hz, $J_2$=8.6 Hz, 1H), 3.06 (d, *J*=2.7 Hz, 1H), 2.04-1.90 (m, 2H), 1.46 (s, 3H), 1.39 (s, 3H), 1.10-1.03 (m, 21H), 0.99 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.9 Hz, 3H), 0.89 (d, *J*=6.9 Hz, 3H), 0.86 (d, *J*=6.9 Hz, 3H)

**Bis aldols 52hc and 53hc**




**51h** **52hc** **53hc**

*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.71 mL, 1.7 mmol, 2.4 M solution in hexanes, 3.3 eq) was added dropwise to a stirred solution of DIA (0.34 mL, 1.8 mmol, 3.6 eq) in THF (10 mL) at 0 °C under nitrogen. After 30 min, a solution of **51h** (0.18 g, 0.51 mmol, 1.0 eq) was added slowly and the mixture was stirred for 2 h at -78 °C. The aldehyde (0.30 g, 2.1 mmol, 4.0 eq) was then added, and, after 20 min, the reaction was quenched with concentrated phosphate buffer (pH 7.5; 10 mL) and extracted with ether (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$. The solvents were removed under reduced pressure, and the diastereoselectivity of the reaction was determined by $^1$H NMR on the crude product by integration of the peaks at 3.43 ppm and 3.35 ppm and was found to be 9 : 91 *anti-trans-anti* to *anti-cis-anti* aldols. The crude reaction mixture was fractionated by FCC (5 - 10 % ethyl acetate in hexane) to give the title aldol **52hc** as a colorless oil (0.20 g, 4.2 $10^{-1}$ mmol, 82 %), **53hc** (11 mg, 2.2 $10^{-2}$ mmol, 4 %) and the recovered starting material **51h** (20 mg, 5.7 $10^{-2}$ mmol, 11 %).

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**52hc**

**$[\alpha]^{24}_D$** -3 (c 0.33, chloroform)

**$R_f$** 0.48 (hexane : ethyl acetate 7 : 3)

**IR** (KBr): 3487, 1709 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.50 (d, *J*=7.4 Hz, 1H), 4.37-4.33 (m, 2H), 4.31-4.27 (m, 1H), 4.11-4.04 (m, 2H), 3.73 (br s, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 3.20-3.10 (m,
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2H), 2.75-2.67 (m, 1H), 2.64-2.56 (m, 1H), 2.04-1.95 (m, 2H), 1.50 (s, 3H), 1.47 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H)

**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 4.81 (dd, $J_1$=2.3 Hz, $J_2$=8.2 Hz, 1H), 4.72 (d, *J*=7.2 Hz, 1H), 4.56 (d, *J*=8.2 Hz, 1H), 4.45 (s, 1H), 4.37 (d, *J*=7.2 Hz, 1H), 4.18 (s, 1H), 3.31-3.08 (m, 2H), 3.18 (s, 3H), 3.16 (s, 3H), 2.33-2.18 (m, 2H), 1.82-1.61 (m, 2H), 1.27 (s, 3H), 1.05 (s, 3H), 1.01-0.89 (m, 15H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.8, 105.5, 98.9, 79.8, 77.9, 76.0, 74.4, 56.0, 55.9, 44.6, 28.9, 28.8, 28.4, 26.0, 25.9, 20.6, 18.3, -4.4, -4.5

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 209.8, 105.8, 99.0, 81.3, 80.4, 77.2, 75.1, 55.7, 55.4, 42.4, 29.0, 27.83, 27.81 26.5, 26.1, 20.3, 18.8, -3.9, -4.0

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 497 ($[M]^+$+1, 56), 465 (44), 407 (8), 366 (17), 334 (98), 317 (100), 276 (44), 185 (20), 159 (32), 119 (72), 75 (84)

**HRMS** *m/z* calcd for $C_{21}H_{40}O_7S_2Si$ 497.2065 (M+H), found 497.2078 (CI)

**53hc**

**$[\alpha]^{27}_D$** -68 (c 1.3, chloroform)

**$R_f$** 0.44 (hexane : ethyl acetate 7 : 3)

**IR** (KBr): 3514, 1738 $cm^{-1}$

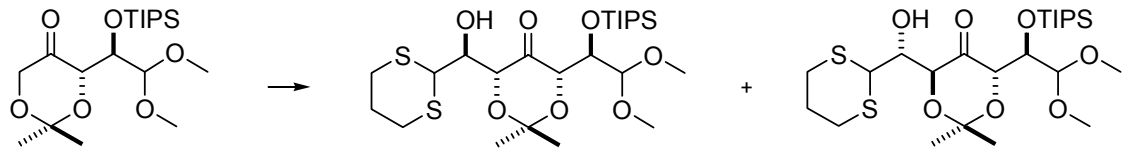
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.51 (d, *J*=7.4 Hz, 1H), 4.45 (dd, $J_1$=1.0 Hz, $J_2$=7.1 Hz, 1H), 4.34 (dd, $J_1$=1.0 Hz, $J_2$=1.8 Hz, 1H), 4.30 (dd, $J_1$=4.3 Hz, $J_2$=7.1 Hz, 1H), 4.04 (dd, $J_1$=1.8 Hz, $J_2$=7.4 Hz, 1H), 4.02 (d, *J*=4.3 Hz, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 3.10-2.98 (m, 2H), 2.70-2.51 (m, 2H), 2.05-1.98 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.4, 105.7, 101.9, 77.5, 74.7, 73.8, 72.7, 56.4, 56.0, 45.4, 28.6, 27.8, 26.0, 25.9, 24.8, 23.7, 18.3, -4.4, -4.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 497 ($[M]^+$+1, 49), 465 (100), 366 (7), 334 (26), 317 (11), 276 (8), 166 (9), 149 (12), 119 (30), 75 (21)

**HRMS** *m/z* calcd for $C_{21}H_{40}O_7S_2Si$ 497.2065 (M+H), found 497.2077 (CI)

**Bis aldols 52hc and 53hc**




**51h** **52hc** **53hc**

*Reaction was done based on the modified procedure L1*

Modified procedure L1 (0.51 mmol scale) gave the mixture of two aldol products. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^{1}$H NMR on the crude product by integration of the peaks at 3.40 ppm and 3.42 ppm and was found to be 74 : 26 of **52hc** to **53hc**. The crude reaction mixture was fractionated by FCC (5 - 10 % ethyl acetate in hexane) to give the title aldol **52hc** as a colorless oil (0.19 g, 0.35 mmol, 69 %) and **53hc** (55 mg, 0.10 mmol, 20 %). Only partial date is reported.

**53hc**

$[\alpha]^{25}_{D}$ -49 (c 1, benzene)

**$^{1}$H NMR** (500 MHz, $C_6D_6$) *δ:* 4.79 (dd, $J_1$=1.0 Hz, $J_2$=7.3 Hz, 1H), 4.71 (d, $J$=7.3 Hz, 1H), 4.64 (ddd, $J_1$=2.4 Hz, $J_2$=3.7 Hz, $J_3$=7.3 Hz, 1H), 4.61 (dd, $J_1$=1.6 Hz, $J_2$=7.3 Hz, 1H), 4.57 (dd, $J_1$=1.0 Hz, $J_2$=1.6 Hz, 1H), 4.01 (d, $J$=3.7 Hz, 1H), 3.43 (dd, $J_1$=1.2 Hz, $J_2$=2.4 Hz, 1H), 3.22 (s, 3H), 3.20 (s, 3H), 3.13-3.06 (m, 1H), 3.01-2.94 (m, 1H), 2.25-2.19 (m, 1H), 2.17-2.10 (m, 1H), 1.77-1.67 (m, 1H), 1.62-1.54 (m, 1H), 1.42 (s, 3H), 1.26 (s, 3H), 1.25-1.17 (m, 3H), 1.18-1.16 (m, 18H)

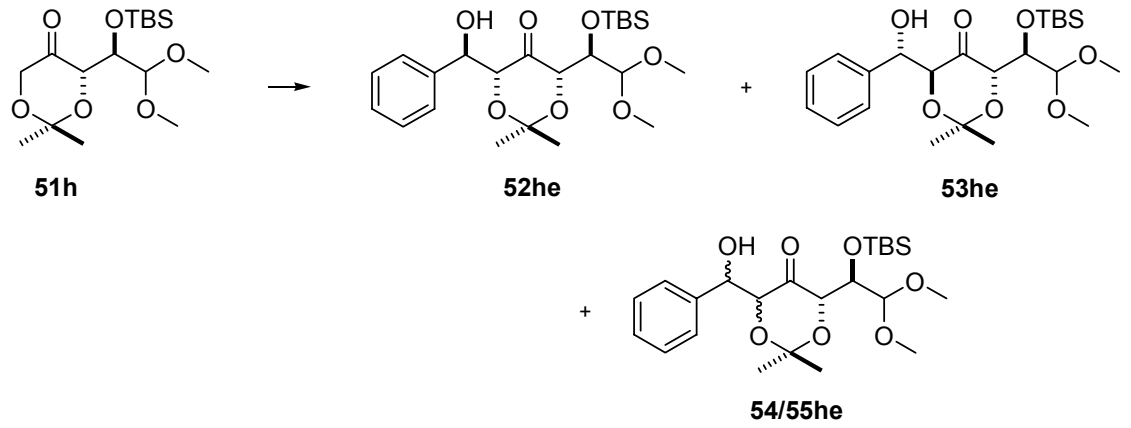
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:*4.49-4.44 (m, 2H), 4.37 (d, $J$=1.0 Hz, 1H), 4.31-4.26 (m, 2H), 4.03 (d, $J$=3.9 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 3.28 (d, $J$=2.4 Hz, 1H), 3.12-3.02 (m, 2H), 2.71-2.58 (m, 2H), 2.05-1.97 (m, 2H), 1.49 (s, 3H), 1.38 (s, 3H), 1.13-0.89 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.1, 105.9, 102.0, 78.3, 74.8, 73.8, 72.4, 56.2, 56.1, 45.5, 28.6, 28.0, 25.9, 24.8, 23.9, 18.3, 12.8

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 539 ($[M+1]^+$, 39), 507 (100), 408 (), 376 (31), 359 (13), 119 (10), 75 (6)

**HRMS** *m/z* calcd for $C_{24}H_{46}O_7S_2Si$ 539.2532 (M+H), found 539.2531 (CI)

**Bis aldol 52he and 53he**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.37 mL, 0.88 mmol, 2.4 M solution in hexanes, 2.2 eq) was added dropwise to a stirred solution of DIA (0.18 mL, 0.96 mmol, 2.4 eq) in THF (10 mL) at 0 °C under nitrogen. After 30 min the solution was cooled down to -78 °C, a solution of **51h** (0.14 g, 0.40 mmol, 1.0 eq) in THF was added slowly, and the mixture was stirred for 40 min at -78 °C. PhCHO (0.11 mg, 0.11 mL, 1.0 mmol, 2.5 eq) was added then and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 10 mL) and extracted with ether (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated, and fractionated by FCC (3 - 7 % ethyl acetate in hexane) to give **53he** (44 mg, 0.10 mmol, 25 %) as a pale yellow liquid and **52he** (90 mg, 0.30 mmol, 50 %) as a white solid. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at δ 5.12 ppm (d, *J*=4.6 Hz) 4.89 ppm (d, *J*=8.4 Hz) 4.78 ppm (d, *J*=8.4 Hz) and was found to be 2 : 64 : 34 of **54**/**55** : **52** : **53**.

*Reaction was done based on the modified procedure B1*

Triethylamine (0.21 mL, 1.5 mmol, 6.0 eq) was dissolved in $CH_2Cl_2$ (5 mL) and the solution was cooled to 0 °C. Dicyclohexylboron chloride (0.75 mL, 0.75 mmol, 3.0 eq,

1.0 M solution in hexane) was added, and the solution was stirred for 15 min. Next, ketone **E32** (87 mg, 0.25 mmol, 1.0 eq) was added as a solution in $CH_2Cl_2$ , and, after stirring for 15 min, benzaldehyde (0.16 mg, 0.15 mL, 1.5 mmol, 6.0 eq) was added. After stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to 0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^{13}C$ NMR on the crude product by integration of the peaks at 101.7 ppm and 98.7 ppm and was found to be 92 : 08 of **53he** : **52he** The products was isolated by FCC (hexane : ethyl acetate 3 - 5 %) to provide a pure bis aldol products in 70 % yield (75 % conversion by $^1H$ NMR).

**52he**

**m.p.** 59-60 °C

**$[\alpha]^{22}_D$** +17 (c 1.5, chloroform)

**$R_f$** 0.57 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 3535, 2929, 1737, 1222, 1108, 837 $cm^{-1}$

**$^1H$ NMR** (500 MHz, $CDCl_3$) *δ:* 7.42-7.24 (m, 5H), 4.89 (d, *J*=8.4 Hz, 1H), 4.59 (d, *J*=7.5 Hz, 1H), 4.44 (dd, $J_1$=1.2 Hz, $J_2$=1.8 Hz, 1H), 4.15 (dd, $J_1$=1.2 Hz, $J_2$=8.4 Hz, 1H), 4.12 (dd, $J_1$=1.8 Hz, $J_2$=7.5 Hz, 1H), 4.06 (br s, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H) 0.90 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H)

**$^{13}C$ NMR** (125 MHz, $CDCl_3$) *δ:* 209.0, 139.8, 128.1, 128.0, 127.6, 105.7, 98.7, 79.8, 79.1, 74.7, 73.7, 56.2, 56.0, 28.8, 26.0, 20.6, 18.4, -4.2, -4.4

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 472 ($[M+18]^+$, 39), 440 (16), 366 (21), 334 (100), 276 (22), 159 (6), 127 (10), 75 (26)

**HRMS** *m/z* calcd for $C_{23}H_{38}O_7Si$ 472.2731 ($M+NH_4$), found 472.2729 (CI)

**53he**

**$[\alpha]^{29}_{D}$** -64 (c 1.85, chloroform)

**$R_f$** 0.61 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 3535, 2930, 1737, 1458, 1375, 1222, 1108, 837 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.41-7.24 (m, 5H), 4.78 (dd, $J_1$=1.7 Hz, $J_2$=8.4 Hz, 1H), 4.52 (d, *J*=7.5 Hz, 1H), 4.31 (dd, $J_1$=1.2 Hz, $J_2$=1.7 Hz, 1H), 4.15 (dd, $J_1$=1.2 Hz, $J_2$=8.4 Hz, 1H), 4.09 (dd, $J_1$=1.7 Hz, $J_2$=7.5 Hz, 1H), 3.63 (d, *J*=1.7 Hz, 1H), 3.45 (s, 3H), 3.37 (s, 3H), 1.32 (s, 3H), 1.17 (s, 3H), 0.88 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H)

**$^{13}$C NMR (**125 MHz, $CDCl_3$) *δ:* 209.4, 139.9, 128.2, 128.0, 127.2, 105.4, 101.7, 77.9, 75.1, 73.8, 72.4, 56.5, 55.5, 26.0, 24.0, 23.5, 18.3, -4.3, -4.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 472 ($[M+18]^+$, 84), 440 (58), 366 (23), 334 (66), 276 (74), 221 (19), 173 (10), 144 (28), 75 (100)

**HRMS** *m/z* calcd for $C_{23}H_{38}O_7Si$ 472.2731 ($M+NH_4$), found 472.2731 (CI)

**54/55he**

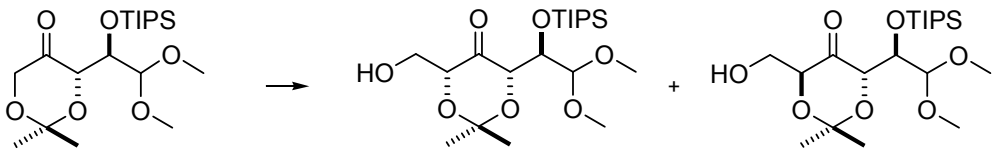
**$[\alpha]^{29}_{D}$** +203 (c 0.4, chloroform)

**$R_f$** 0.44 (hexane : ethyl acetate 4 : 1)

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.44-7.40 (m, 5H), 5.12 (dd, $J_1$=4.5 Hz, $J_2$=5.0 Hz, 1H), 4.51 (d, *J*=7.5 Hz, 1H), 4.34 (dd, $J_1$=1.1 Hz, $J_2$=4.5 Hz, 1H), 4.31 (dd, $J_1$=1.1 Hz, $J_2$=1.7 Hz, 1H), 4.02 (dd, $J_1$=1.7 Hz, $J_2$=7.5 Hz, 1H), 3.40 (s, 3H), 3.19 (s, 3H), 2.72 (d, *J*=5.0 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H) 0.84 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 205.4, 140.4, 128.4, 128.0, 127.1, 105.2, 102.0, 78.1, 76.7, 73.5, 70.5, 56.4, 55.2, 26.0, 24.5, 23.8, 18.3, -4.4, -4.7

**Bis aldol 52fa and 53fa**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.23 mL, 0.55 mmol, 2.4 M solution in hexanes, 3.3 eq) was added dropwise to a stirred solution of DIA (0.11 mL, 0.60 mmol, 3.6 eq) in THF (5 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **51f** (65 mg, 0.17 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 2 h at -78 °C. Formaldehyde gas (excess) was added then and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 5 mL) and extracted with ether (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated, and fractionated by PTLC (hexanes : ethyl acetate 4 : 1) to give the mixture of *cis* and *trans* isomers as pale yellow liquid (20 mg, 0.050 mmol, 29 %, 39 % BORSM). Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at δ 3.34 ppm and 3.33 ppm and was found to be 30 : 70 of **53fa** to **52fa** (tentatively assigned).

**52fa**

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.52 (d, *J*=7.3 Hz, 1H), 4.39 (dd, $J_1$=0.9 Hz, $J_2$=1.7 Hz, 1H), 4.36 (dd, $J_1$=1.7 Hz, $J_2$=7.3 Hz, 1H), 4.30 (ddd, $J_1$=0.9 Hz, $J_2$=5.5 Hz, $J_3$=6.7 Hz, 1H), 3.92-3.82 (m, 1H), 3.82-3.75 (m, 1H), 3.40 (s, 3H), 3.33 (s, 3H), 2.35 (br s, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.21-1.01 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 204.7, 105.6, 98.7, 80.3, 77.8, 73.7, 62.8, 55.8, 55.6, 29.1, 20.4, 18.2, 12.8

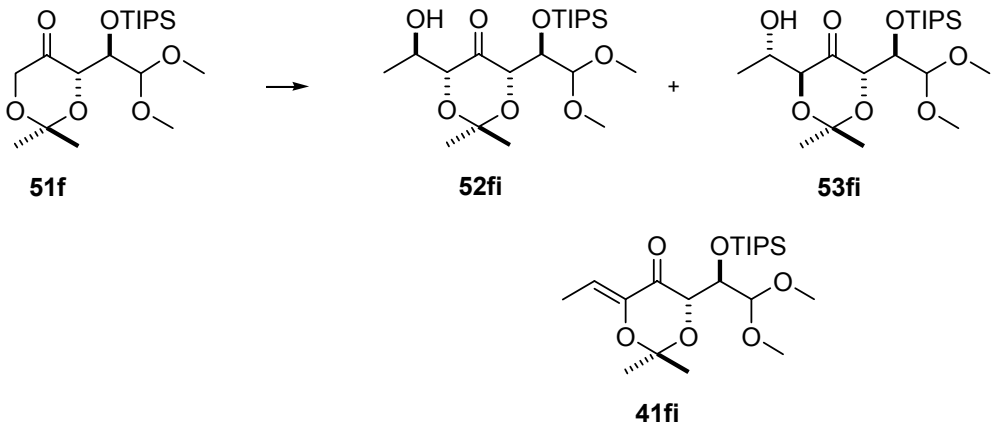
**53fa**

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.50 (d, *J*=7.3 Hz, 1H), 4.33 (dd, $J_1$=1.1 Hz, $J_2$=1.5 Hz, 1H), 4.31(dd, $J_1$=1.1 Hz, $J_2$=7.3 Hz, 1H), 4.25 (ddd, $J_1$=1.2 Hz, $J_2$=5.6 Hz, $J_3$=6.5 Hz, 1H), 3.92-3.82 (m, 1H), 3.82-3.75 (m, 1H), 3.41 (s, 3H), 3.34 (s, 3H), 2.11 (br s, 1H), 1.49 (s, 3H), 1.41 (s, 3H), 1.21-1.01 (m, 21H)
**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.2, 105.7, 101.6, 78.5, 73.6, 73.3, 60.9, 55.9, 55.7, 24.8, 24.0, 18.3, 12.8

The measurements done on the mixture of the two isomers due to the problem with separation

**IR** (KBr): 3478, 2943, 2866, 1720, 1464, 1382, 1122, 1056 cm-1
**LRMS** (CI), *m/z* (relative intensity): 438 ($[M+18]^+$, 37), 406 (100), 389 (69), 362 (45), 322 (23), 168 (33), 75 (46)
**HRMS** *m/z* calcd for $C_{20}H_{40}O_7Si$ 345.2097 (M – $CH(OCH_3)_2$), found 345.1733 (EI)
**HRMS** *m/z* calcd for $C_{20}H_{40}O_7Si$ 421.2622 (M + H), found 421.2447 (EI)

**Bis aldol 52fi and 53fi**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.35 mL, 0.85 mmol, 2.4 M solution in hexanes, 3.3 eq) was added dropwise to a stirred solution of DIA (0.17 mL, 0.92 mmol, 3.6 eq) in THF (10 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **51f** (89 mg, 0.26 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 2 h at -78 °C. Freshly distilled acetaldehyde (45 mg, 1.0 mmol, 4.0 eq) was added and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 5 mL) and extracted with ether (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$ and concentrated. Diastereoselectivity of the reaction was measured on the crude reaction mixture by integration of peaks in $^1$H NMR at δ 4.56 ppm and 4.52 ppm and was found to be 83 : 17 of **52fi** to **53fi** Crude product fractionated by chromatography column (hexanes : ethyl acetate 5-10 %) to give the recovered staring material **51f** (2.00 mg, 2 %), α β-unsaturated ketone **41fi** (18 mg, 5.0 $10^{-1}$ mmol, 19 %) as a colorless oil and inseparable mixture of **52fi** and **53fi** (79 mg, 0.20 mmol, 79 %, BORSM 81 %) as a colorless oil. Further purification provided only partial separation of the two diastereoisomers.

**52fi**

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.55 (d, *J*=7.5 Hz, 1H), 4.38 (dd, $J_1$=1.0 Hz, $J_2$=2.6 Hz, 1H), 4.12-4.04 (m, 2H), 3.89 (dd, $J_1$=1.0 Hz, $J_2$=7.5 Hz, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 3.31 (br s, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 1.21 (d, *J*=6.2 Hz, 3H), 0.87 (s, 9H), 0.10 (s 3H), 0.08 (s 3H)

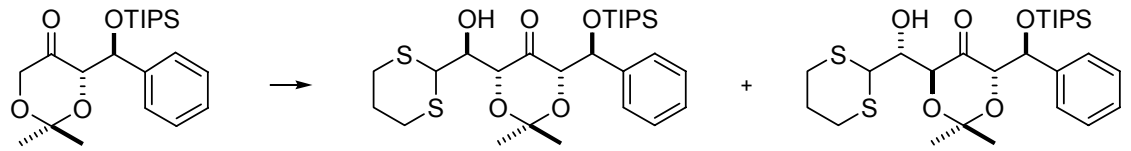
**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.5, 105.7, 98.7, 80.3, 79.6, 74.5, 68.0, 56.3, 55.9, 29.0, 26.1, 20.7, 18.9, 18.4, -4.3, -4.4

**53fi**

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.50 (d, *J*=7.6 Hz, 1H), 4.25 (d, *J*=0.8 Hz, 1H), 4.10-4.05 (m, 1H), 3.89-3.91 (m, 1H), 3.83 (dd, $J_1$=0.8 Hz, $J_2$=7.6 Hz, 1H), 3.54 (s, 3H), 3.45 (s, 3H), 3.07 (br s, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.21 (d, *J*=6.2 Hz, 3H), 0.85 (s, 9H), 0.04 (s 3H), 0.01 (s 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 209.4, 105.5, 101.5, 77.7, 75.9, 73.7, 66.5, 55.4, 55.6, 26.2, 26.0, 24.4, 23.7, 18.7, 18.3, -4.4, -4.7

**Bis aldol 52ec and 53ec**




**51e** **52ec** **53ec**

*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.10 mL, 0.24 mmol, 2.2 M solution in hexanes, 3.3 eq) was added dropwise to a stirred solution of DIA (0.050 mL, 0.25 mmol, 3.6 eq) in THF (3 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **51e** (27 mg, 0.70 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 2 h at -78 °C. Freshly distilled benzaldehyde was added (42 mg, 0.28 mmol, 4.0 eq) and then and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 5 mL) and extracted with ether (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated, and fractionated by PTLC (hexane : ethyl acetate 10 % x 2) to give **52ec** (20 mg, 0.040 mmol, 54 %) as a pale yellow oil and **53ec** (12 mg, 0.020 mmol, 32 %) as pale yellow liquid. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at δ 5.27 ppm (*J*=3.1 Hz) and 5.25 ppm (*J*=2.9 Hz) or by $^{13}$C NMR by integration of peaks at δ 99.1 ppm and 101.9 ppm and was found to be 63 : 37 of **52ec** to **53ec**.

**52ec**

**$[\alpha]^{25}_D$** +1 (c 1, chloroform)

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.35-7.19 (m, 5H), 5.27 (d, *J*=3.1 Hz, 1H), 4.60 (dd, $J_1$=1.3 Hz, $J_2$=3.1 Hz, 1H), 4.29 (dd, $J_1$=1.0 Hz, $J_2$=8.2 Hz, 1H), 3.87 (d, *J*=3.9 Hz, 1H), 3.82 (dd, $J_1$=1.8 Hz, $J_2$=3.9 Hz, 1H), 3.06-2.91 (m, 2H), 3.00 (d, *J*=1.8 Hz, 1H), 2.58-2.47 (m, 2H), 1.99-1.90 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.09-1.00 (m, 3H), 0.99 (d, *J*=7.0 Hz, 9H), 0.94 (d, *J*=7.0 Hz, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.9, 140.2, 128.4, 128.2, 127.7, 99.1, 82.4, 76.9, 75.32, 75.30, 44.5, 28.8, 28.2, 27.5, 25.7, 21.4, 18.2, 18.1, 12.5

**53ec**

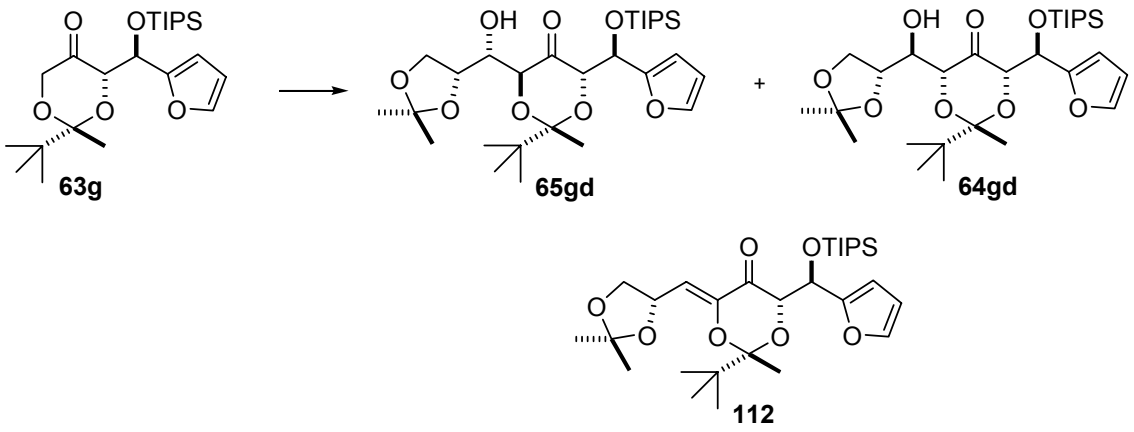
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.39-7.17 (m, 5H), 5.25 (d, *J*=2.8 Hz, 1H), 4.67 (dd, $J_1$=1.3 Hz, $J_2$=2.8 Hz, 1H), 4.41 (ddd, $J_1$=2.0 Hz, $J_2$=4.6 Hz, $J_3$=6.6 Hz, 1H), 4.27 (dd, $J_1$=1.3 Hz, $J_2$=4.6 Hz, 1H), 3.83 (d, *J*=6.6 Hz, 1H), 3.05 (d, $J_1$=2.0 Hz, 1H), 3.02-2.95 (m, 1H), 2.88-2.81 (m, 1H), 2.56-2.48 (m, 1H), 2.45-2.38 (m, 1H), 2.06-1.91 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H), 1.09-0.99 (m, 3H), 0.98 (d, *J*=7.0 Hz, 9H), 0.94 (d, *J*=7.0 Hz, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.84, 140.4, 128.1, 127.7, 127.6, 101.9, 79.1, 74.8, 73.7, 73.0, 43.9, 27.0, 26.0, 25.4, 24.3, 23.9, 18.2, 18.1, 12.5

**LRMS** (CI), *m/z* (relative intensity): 541 ($[M+1]^+$, 23), 309 (7), 363 (100), 219 (20), 185 (5), 148 (6), 119 (21)

**HRMS** *m/z* calcd for $C_{27}H_{44}O_5S_2Si$ 541.2478 (M+H), found 541.2491 (CI)

**Bis aldols 64gd and 65gd**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.15 mL, 0.34 mmol, 2.3 M solution in hexanes, 3.3 eq) was added dropwise to a stirred solution of DIA (0.070 mL, 0.37 mmol, 3.6 eq) in THF (3 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **63g** (40 mg, 0.090 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 2 h at -78 °C. (*R*)-glyceraldehyde freshly prepared (81 mg, 0.62 mmol, 6.0 eq) was added then and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 5 mL) and extracted with ether (x 4). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated, and fractionated by FCC (hexanes : ethyl acetate 3 - 10%) to give the α, β - unsaturated product **112** (13 mg, 26 %), recovered starting material **63g** (11 mg, 28 %), **65gd** aldol product (16 mg, 30 %, BORSM 41 %) as a pale yellow liquid, **64gd** (6.0 mg, 12 %, BORSM 16 %) as pale yellow liquid. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at δ 5.41(d, *J*=3.9 Hz, 1H) and 5.34 (d, *J*=2.5 Hz, 1H) and was found to be 17 : 83 of **64gd** to **65gd**. No effort was made to assign the *cis*/*trans* configuration.

*Reaction was done based on the modified procedure B1*

Triethylamine (0.14 mL, 1.0 mmol, 6.2 eq) was dissolved in $CH_2Cl_2$ (5 mL) and the solution was cooled to 0 °C. Dicyclohexylboron chloride (0.50 mL, 0.50 mmol, 3.1 eq, 1.0 M solution in hexane) was added, and the solution was stirred for 15 min. Next, ketone **63g** (67 mg, 0.16 mmol, 1.0 eq) was added as a solution in $CH_2Cl_2$ , and, after stirring for 15 min, freshly prepared (*R*)-glyceraldehyde (73 mg, 0.56 mmol, 3.5 eq) was added. After stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol and cooled to 0 °C. Concentrated pH 7 buffer and hydrogen peroxide (30 %) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1$H NMR on the crude product by integration of the peaks at δ 5.41 (d, *J*=3.9 Hz, 1H) and 5.34 (d, *J*=2.5 Hz, 1H) and was found to be 25 : 75 of **65gd** to **64gd**. No effort was made to assign the *cis*/*trans* configuration. The products was isolated by FCC (hexane : ethyl acetate 95 : 5) to provide **65gd** (52 mg, 0,090 mmol, 60 %) as a pale yellow liquid and **64gd** (15 mg, 0.030 mmol 17 %) as pale yellow liquid.

**65gd**

**$[\alpha]^{23}_D$** -55 (c 0.9, chloroform)

**Rf** 0.38 (hexane : ethyl acetate 4 : 1)

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.31-7.28 (m, 1H), 6.37-6.34 (m, 1H), 6.32-6.29 (m, 1H), 5.34 (d, *J*=2.6 Hz, 1H), 4.47 (dd, $J_1$=0.7 Hz, $J_2$=2.6 Hz, 1H), 4.29 (ddd, $J_1$=4.3 Hz, $J_2$=6.8 Hz, $J_3$=7.6 Hz, 1H), 4.12 (dd, $J_1$=0.7 Hz, $J_2$=8.1 Hz, 1H), 3.98 (dd, $J_1$=6.8 Hz, $J_2$=8.0 Hz, 1H), 3.86 (dd, $J_1$=7.6 Hz, $J_2$=8.0 Hz, 1H), 3.73 (ddd, $J_1$=3.6 Hz, $J_2$=4.3 Hz, $J_3$=8.1 Hz, 1H), 2.90 (d, *J*=3.6 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.12-0.97 (m, 21H), 0.96 (s, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 209.7, 153.2, 141.5, 110.6, 109.2, 108.5, 105.8, 79.8, 76.1, 75.1, 70.1, 69.9, 65.9, 41.2, 26.6, 25.7, 18.2, 18.14, 18.07, 12.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 572 ($[M]^+$+18, 9), 381 (4), 253 (100), 193 (33), 148 (13), 131 (15), 118 (19), 96 (18), 58 (30)

**HRMS** *m/z* calcd for $C_{29}H_{50}O_8Si$ 572.3619 (M + 18), found 572.3636 (CI, $NH_3$)

**64gd**

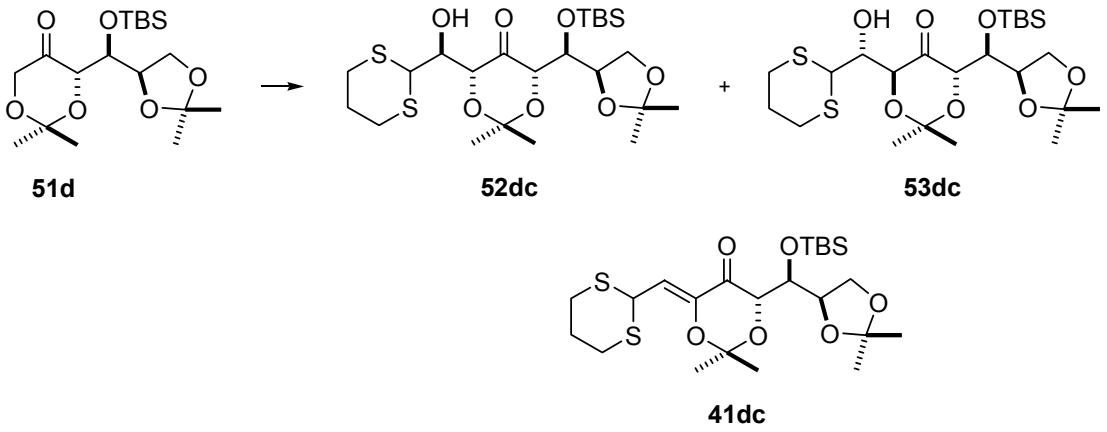
**$[\alpha]^{23}_D$** +16 (c 1, chloroform)

**Rf** 0.28 (hexane : ethyl acetate 4 : 1)

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.28-7.26 (m, 1H), 6.31-6.26 (m, 2H), 5.41 (d, *J*=3.8 Hz, 1H), 4.54 (dd, $J_1$=1.0 Hz, $J_2$=3.8 Hz, 1H), 4.36 (dd, $J_1$=1.0 Hz, $J_2$=4.7 Hz, 1H), 4.24-4.15 (m, 1H), 3.99-3.90 (m, 3H), 2.56 (d, *J*=2.6 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.04-0.97 (m, 21H), 0.88 (s, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 206.0, 153.6, 141.4, 110.4, 109.2, 108.5, 102.8, 81.0, 78.0, 75.4, 72.5, 69.3, 65.8, 39.6, 26.7, 25.4, 24.9, 18.14, 18.07, 18.0, 12.5

**Bis aldols 52dc and 53dc**




*Reaction was done based on the modified procedure L1*

*n*-BuLi (0.52 mL, 1.3 mmol, 2.4 M solution in hexanes, 2.2 eq) was added dropwise to a stirred solution of DIA (0.26 mL, 1.4 mmol, 2.4 eq) in THF (10 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **51d** (0.22 g, 0.57 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 30 min at -78 °C. After this time (0.23 g, 1.5 mmol, 2.7 eq) was added then and after 20 min the reaction was quenched with concentrated phosphate buffer (pH 7.5; 5 mL) and extracted with ether (x 4). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated, and fractionated by FCC (hexane : ethyl acetate 5 – 10 %) to give the unsaturated product **41dc** (25 mg, 0.050 mmol, 9 %), recovered starting material **51d** (37 mg, 0.10 mmol, 17 %) and **52dc** aldol product (0.20 g, 0.38 mmol, 67 %, BORSM 81 %) as a colorless liquid. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR (in $CDCl_3$) at δ 1.50 ppm, 1.45 ppm and was found to be 91 : 9 of **52dc : 53dc**.

**52dc**

**IR** (KBr): 3447, 2985, 2930, 1717 $cm^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 4.78 (dd, $J_1$=3.9 Hz, $J_2$=7.0 Hz, 1H), 4.57 (dd, $J_1$=1.0 Hz, $J_2$=7.0 Hz, 1H), 4.45 (ddd, $J_1$=6.6 Hz, $J_2$=8.2 Hz, $J_3$=8.2 Hz, 1H), 4.16 (d, $J$=3.9 Hz, 1H), 4.10 (dd, $J_1$=2.8 Hz, $J_2$=8.2 Hz, 1H), 4.05 (dd, $J_1$=6.6 Hz, $J_2$=8.1 Hz, 1H), 3.92 (dd, $J_1$=1.0 Hz, $J_2$=2.8 Hz, 1H), 3.58 (dd, $J_1$=8.1 Hz, $J_2$=8.2 Hz, 1H) 3.49 (br s, 1H), 3.08-3.02 (m, 1H), 2.99-2.93 (m, 1H), 2.21-2.15 (m, 1H), 2.13-2.06 (m, 1H), 1.75-1.65 (m, 1H), 1.58-1.51 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.10 (s, 9H), 0.99 (s, 3H), 0.32 (s, 3H), 0.27 (s, 3H)

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.43-4.20 (m, 2H), 4.22 (ddd, $J_1$=4.6 Hz, $J_2$=8.1 Hz, $J_3$=8.1 Hz, 1H), 4.10 (d, $J$=2.8 Hz, 1H), 4.06-4.04 (m, 1H), 4.03-3.99 (m, 2H), 3.63 (dd, $J_1$=8.1 Hz, $J_2$=8.2 Hz, 1H), 3.31 (br s, 1H), 3.13-3.03 (m, 2H), 2.68-2.55 (m, 2H), 2.06-1.97 (m, 2H), 1.50 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 208.9, 109.5, 99.2, 80.3, 78.3, 78.2, 78.1, 78.0, 77.1, 42.9, 28.8, 27.3, 27.2, 27.0, 26.8, 26.1, 25.8, 20.6, 19.1, -3.4, -3.8

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 208.2, 109.2, 99.1, 79.8, 77.5, 77.2, 76.1, 75.9, 66.5, 44.3, 28.7, 28.0, 27.6, 26.9, 26.3, 25.7, 21.0, 18.6, -3.9, -4.3

**41dc**

**IR** (KBr): 2988, 1713, 1623 $cm^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 6.49 (d, $J$=10.8 Hz, 1H), 5.08 (d, $J$=10.8 Hz, 1H), 4.61 (ddd, $J_1$=6.5 Hz, $J_2$=8.0 Hz, $J_3$=8.1 Hz, 1H), 4.12 (dd, $J_1$=1.8 Hz, $J_2$=8.1 Hz, 1H), 4.06 (dd, $J_1$=6.5 Hz, $J_2$=8.0 Hz, 1H), 3.99 (d, $J$=1.8 Hz, 1H), 3.56 (dd, $J_1$=8.0 Hz, $J_2$=8.0 Hz, 1H), 2.39-2.30 (m, 2H), 2.26-2.16 (m, 2H), 1.43-1.40 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 1.09 (s, 9H), 1.06 (s, 3H), 0.30 (s, 3H), 0.26 (s, 3H)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 191.1, 146.3, 113.3, 109.8, 101.1, 79.2, 78.0, 77.4, 66.6, 38.5, 28.4, 28.3, 28.2, 27.2, 26.7, 26.6, 26.0, 24.4, 23.2, 19.0, -3.8, -4.0

**LRMS** (EI), *m/z* (relative intensity): 505 ($[M]^+$+1, 1), 504 (2), 447 (51), 389 (24), 346 (49), 185 (33), 133 (100), 101 (71), 73 (99)

**HRMS** *m/z* calcd for $C_{23}H_{40}O_6S_2Si$ 504.2036 (M), found 504.2041 (EI)

### 3.8 Studies towards synthesis of carbohydrates and their derivatives

**General experimental procedure for reduction of bisaldol product into corresponding alcohol with $NaBH(OAc)_3$.**

**Method 1 is based on modified procedure from ref.[17]**

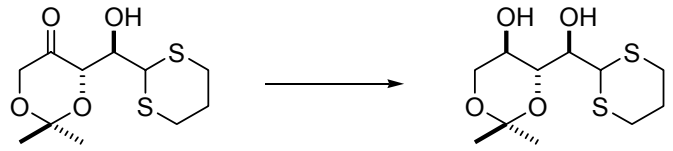
To a solution of β-hydroxyketone (1.0 eq) in dry $CH_2Cl_2$ (0.40 mL/mmol) AcOH (0.17 eq) and $NaBH(OAc)_3$ (1.2 eq) were added at -20 °C. Reaction was kept at that temperature for 1 - 5 d (TLC controlled).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (x 3).The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a crude diols mixture which was purified by flash column chromatography using silica gel (hexane : ethyl acetate 10 - 50 %) to give pure products.

**General experimental procedure for reduction of bisaldol product into corresponding alcohol with $NaBH_4$**

**Method 2**

To a solution of β-hydroxyketone (1.0 eq) in MeOH, $NaBH_4$ (2.0 eq) was added at 0 ° C. Reaction was warmed up to r.t. and stirred at that temperature for 8 - 12h (TLC controlled).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with AcOEt (x 3).The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a crude diols mixture which was purified by flash column chromatography using silica gel (hexane : ethyl acetate 10 - 50%) to give pure products.

**(4R,5R)-4-[(*R*)-(1,3-dithian-2-yl)(hydroxy)methyl]-2,2-dimethyl-1,3-dioxan-5-ol (72b)**




**7c** **72b**

To a solution of β-hydroxyketone **7c** (0.45 g, 1.6 mmol, 1.0 eq) in dry $CH_2Cl_2$ (2.5 mL), AcOH (0.50 mL) and $NaBH(OAc)_3$ (0.41 g, 1.9 mmol, 1.2 eq) were added at -20 °C. Reaction was stirred at -20 °C for 12 h then kept at that temperature for 1 d (TLC controlled). The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (x 3).The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a mixture of diols in ratio 2 : 98 of *anti* : *syn* (by $^1$H NMR), which was purified by FCC using silica gel (hexane : ethyl acetate 30 %) to give pure product **72b** (0.43 g, 1.5 mmol, 96 %).

**72b**

**mp** 60-61 °C

**$[\alpha]^{23}_D$** -79 (c 2, chloroform)

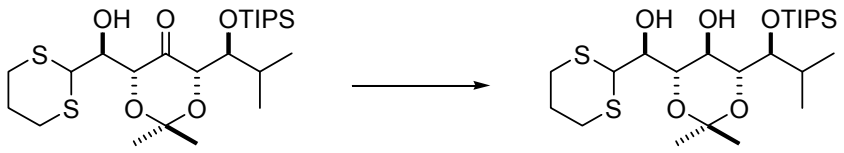
**$R_f$** 0.56 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 3410, 2910, 2820, 1478, 1456, 1103 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.42 (d, *J*=3.1 Hz, 1H,), 3.95 (m, 1H), 3.90 (m, 2H), 3.82 (m, 1H), 3.64 (dd, $J_1$=8.8 Hz, $J_2$=11.4 Hz, 1H), 3.36 (d, *J*=1.9 Hz, 1H), 3.05 (d, *J*=3.8 Hz, 1H), 2.93 (m, 1H), 2.83 (m, 1H), 2.10 (m, 1H), 1.91 (m, 1H), 1.48 (s, 3H), 1.37 (s, 3H).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 99.2, 78.5, 71.8, 67.2, 64.2, 49.1, 29.8, 29.0, 28.5, 26.0, 19.7

**Diol 74fc**




**52fc** **74fc**

Procedure 1 (0.20 mmol scale) gave the crude diols mixture. Diastereoselectivity of the reaction was measured by integrating peaks at 1.36 ppm and 1.31 ppm and was found to be 1 : 16 *anti* to *syn*. The crude mixture was purified by PTLC (hexane : ethyl acetate 3 : 2) to give pure **74fc** as a colorless oil in 94 % yield. Assignment of the stereochemistry was accomplished based on $^{1}$H NMR chemical shift and coupling constants. Based on this data relative configuration of the rest of related compound was established.

**IR** (KBr): 3466, 2940, 2866, 1464, 1066, 883 cm$^{-1}$

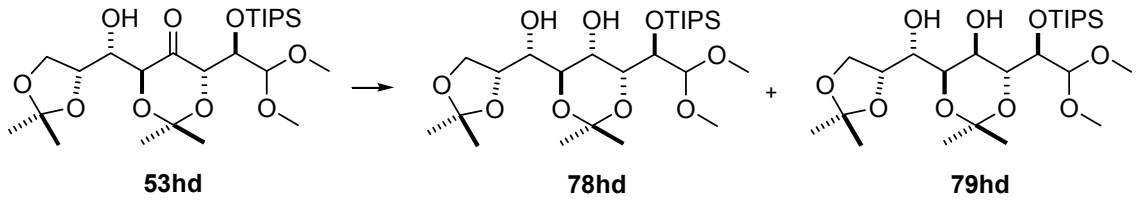
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.16 (d, *J*=2.9 Hz, 1H), 4.12 (dd, $J_1$=2.9 Hz, $J_2$=7.5 Hz, 1H), 3.94 (dd, $J_1$=7.5 Hz, $J_2$=8.7 Hz, 1H), 3.91 (br s, 1H), 3.86 (dd, $J_1$=4.0 Hz, $J_2$=5.3 Hz, 1H), 3.81 (d, *J*=0.8 Hz, 1H), 3.77 (ddd, $J_1$=0.8 Hz, $J_2$=8.7 Hz, $J_3$=9.2 Hz, 1H), 3.73 (dd, $J_1$=5.3 Hz, $J_2$=9.2 Hz, 1H), 3.17-3.05 (m, 2H), 2.81-2.73 (m, 1H), 2.70-2.62 (m, 1H), 2.07-1.97 (m, 2H), 1.97-1.88 (m, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 1.08 (m, 3H), 1.08 (s, 18H) 0.96 (d, *J*=6.7 Hz, 3H), 0.96 (d, *J*=7.0 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 99.1, 81.2, 80.7, 71.5, 71.2, 69.9, 46.3, 34.0, 29.5, 29.1, 28.6, 26.2, 19.3, 19.0, 18.4, 18.3, 16.2, 13.2

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 509 ([M+1]$^{+}$, 100), 468 (16), 451 (61), 277 (16), 215 (15), 119 (19)

**HRMS** *m/z* calcd for $C_{24}H_{48}O_5S_2Si$ 509.2791 (M+H), found 509.2784 (CI)

**Diol 78hd**



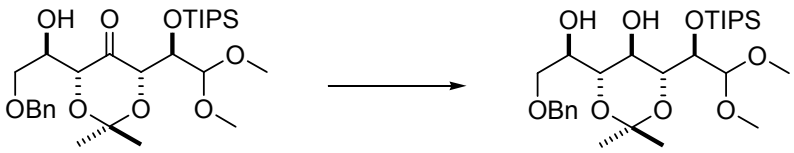

**53hd** **78hd** **79hd**

Modified reduction procedure 1 (0.14 g, 0.27 mmol) gave the mixture of *syn* and *anti* diols. The diastereoselectivity of the reaction was measured by integration of peaks in $^1$H NMR: 1.31 ppm and 1.29 ppm and was found to be 17 : 83 (1 : 5) of **79hd** to **78hd**. Purification of the reaction mixture by FCC (hexane : ethyl acetate 4 : 1) provided pure *syn* diol **78hd** (77 mg, 0.15 mmol) in 55 % yield. Only partial data is reported.

**78hd**

**$^1$H NMR** (500 MHz, $C_6D_6$-$D_2O$, 2 x OH removed) $\delta$: 4.55 (dd, $J_1$=4.2 Hz, $J_2$=6.6 Hz, 1H), 4.51 (d, $J$=5.5 Hz, 1H), 4.44 (dd, $J_1$=4.5 Hz, $J_2$=5.5 Hz, 1H), 4.31 (ddd, $J_1$=4.5 Hz, $J_2$=6.9 Hz, $J_3$=6.9 Hz 1H), 4.19 (dd, $J_1$=4.2 Hz, $J_2$=4.5 Hz, 1H), 3.93 (dd, $J_1$=6.9 Hz, $J_2$=7.8 Hz, 1H), 3.90 (dd, $J_1$=6.9 Hz, $J_2$=7.8 Hz, 1H), 3.85 (dd, $J_1$=6.6 Hz, $J_2$=6.8 Hz, 1H), 3.59 (dd, $J_1$=4.5 Hz, $J_2$=6.8 Hz, 1H), 3.18 (s, 3H), 3.12 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 1.25-1.19 (m, 21H)

**Diol 74hb**



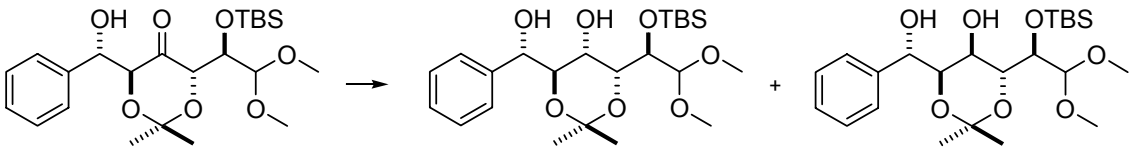

**52hb** **74hb**

Modified procedure 1 (0.060 mmol scale) gave a crude mixture of diols in 1 : 19) *anti* to *syn* ratio. It was which was purified by PTLC (hexane : ethyl acetate 7 : 3) to give pure **74hb** as a colorless oil in 99 % yield. Only partial date is reported.

**74hb**

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 7.32-7.25 (m, 5H), 4.60 (d, $J$=12.0 Hz, 1H), 4.53 (d, $J$=12.0 Hz, 1H), 4.42 (d, $J$=1.0 Hz, 1H), 4.35 (d, $J$=4.5 Hz, 1H), 3.89 (dd, $J_1$=1.0 Hz, $J_2$=4.5 Hz 1H), 3.96 (dddd, $J_1$=2.6 Hz, $J_2$=2.7 Hz, $J_3$=6.0 Hz, $J_4$=6.4 Hz, 1H), 3.88 (dd, $J_1$=1.0 Hz, $J_2$=9.2 Hz, 1H), 3.86 (ddd, $J_1$=1.0 Hz, $J_2$=9.0 Hz, $J_3$=9.2 Hz, 1H), 3.74 (dd, $J_1$=6.4 Hz, $J_2$=9.0 Hz, 1H), 3.67 (dd, $J_1$=2.7 Hz, $J_2$=10.0 Hz, 1H), 3.60 (dd, $J_1$=6.1 Hz, $J_2$=10.0 Hz, 1H), 3.53 (s, 3H), 3.45 (s, 3H), 3.32 (d, $J$=2.7 Hz, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.08 (m, 21H)

**Diol 78he and 79hd**




**53he** **78he** **79he**

Modified procedure 1 (0.10 mmol scale) give a crude mixture of diols. Diastereoselectivity was measured by integration of characteristic peaks in $^{1}$H NMR at 4.81 ppm and 4.76 ppm and was found to be 4.3 : 1 of *syn* : *anti* products. The crude was purified by PTLC (hexane : ethyl acetate 3: 2) to give **78he** as a colorless oil (30 mg, 7.0 $10^{-2}$ mmol, 66 % yield) and **79hd** as a colorless oil (6.0 mg, 1.0 $10^{-2}$ mmol, 13 % yield).

**78he**

**$[\alpha]^{23}_{D}$** +19 (c 1.21, chloroform)

**$R_f$** 0.19 (hexane : ethyl acetate 4 : 1)

**$R_f$** 0.32 (hexane : ethyl acetate 7 : 3)

**IR** (KBr): 3466, 2986, 2930, 2856, 1459, 1379, 1249, 1225, 1170, 1072, 836, 780, 700 $cm^{-1}$

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.43-7.25 (m, 5H), 4.81 (dd, $J_1$=2.9 Hz, $J_2$=5.8 Hz, 1H), 4.42 (d, *J*=6.1 Hz, 1H), 4.10 (dd, $J_1$=4.1 Hz, $J_2$=6.4 Hz, 1H), 3.94 (br s, 1H), 3.93 (dd, $J_1$=4.3 Hz, $J_2$=6.1 Hz, 1H), 3.83 (dd, $J_1$=4.1 Hz, $J_2$=4.3 Hz, 1H), 3.74 (dd, $J_1$=5.8 Hz, $J_2$=6.4 Hz, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 2.99 (d, *J*=2.9 Hz, 1H), 1.28 (s, 3H), 1.27 (s, 3H) 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 140.4, 128.3, 127.8, 127.0, 105.6, 101.3, 77.9, 75.2, 74.8, 71.1, 69.6, 56.6, 56.0, 26.1, 25.0, 24.0, 18.5, -4.5, -4.9

**LRMS** (CI), *m/z* (relative intensity): 474 ($[M+NH_4]^+$, 3), 457 (2), 442 (9), 410 (12), 385 (18), 384 (100), 367 (48), 352 (11), 335 (11), 161 (13), 75 (24)

**HRMS** *m/z* calcd for $C_{23}H_{40}O_7Si$ 474.2887 ($M+NH_4$), found 474.2906(CI)

**79he**

**$[\alpha]^{28}_{D}$** +3 (c 0.4, chloroform)

**$R_f$** 0.24 (hexane : ethyl acetate 7 : 3)

**IR** (KBr): 3476, 2988, 2930, 2856, 1464, 1379, 1251, 1060, 837 $cm^{-1}$

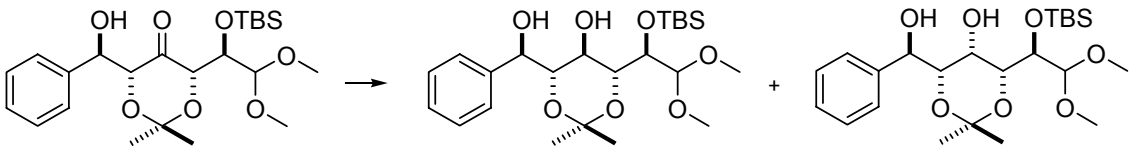
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.41-7.22 (m, 5H), 4.76 (dd, $J_1$=2.6 Hz, $J_2$=6.8 Hz, 1H), 4.27 (d, *J*=2.2 Hz, 1H), 4.08 (ddd, $J_1$=3.0 Hz, $J_2$=3.1 Hz, $J_3$=6.3 Hz, 1H), 3.86 (dd, $J_1$=2.2 Hz, $J_2$=8.6 Hz, 1H), 3.73 (dd, $J_1$=3.3 Hz, $J_2$=8.6 Hz, 1H), 3.66 (dd, $J_1$=6.9 Hz, $J_2$=6.9 Hz, 1H), 3.52 (s, 3H), 3.45 (d, *J*=2.6 Hz, 1H), 3.44 (s, 3H), 3.16 (d, *J*=3.1 Hz, 1H), 1.26 (s, 3H), 1.19 (s, 3H) 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 141.2, 128.2, 127.7, 127.1, 108.5, 101.6, 75.8, 75.6, 73.1, 72.9, 70.5, 58.6, 56.5, 26.1, 24.3, 24.0, 18.4, -4.0, -4.7

**LRMS** (CI), *m/z* (relative intensity): 474 ($[M+18]^+$, 25), 457 ($[M+1]^+$, 13), 442 (73), 425 (57), 410 (100), 384 (28), 367 (3), 352 (15), 161 (5), 75 (21)

**HRMS** *m/z* calcd for $C_{23}H_{40}O_7Si$ 474.2887 ($M+NH_4$), found 474.2898(CI)

**Diol 74he**




Procedure 1 gave the give a crude mixture. Diastereoselectivity of the reaction was measured by integrating peaks at 1.46 ppm and 1.38 ppm and was found to be 1 : 30 *anti* to *syn*. The crude mixture was purified by flash column chromatography using silica gel (hexane : ethyl acetate 7 : 3) to give pure **74he** as a colorless oil in 83 % yield.

Procedure 2 gave the give a crude mixture of diols. Diastereoselectivity of the reaction was measured by integrating peaks at 1.46 ppm and 1.38 ppm and was found to be 1 : 2.2 *anti* to *syn*. The crude mixture was purified by flash column chromatography using silica gel (hexane : ethyl acetate 7 : 3) to give pure **74he** as a colorless oil in 55 % yield and **75he** as a white solid in 25 % yield.

**74he**

**$[\alpha]^{24}_{D}$** +7 (c 0.99, chloroform)

**$R_f$** 0.31 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 3412, 2992, 2929, 2855, 1459, 1380, 1255, 1203, 1152, 1069, 1002, 889, 778, 700 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.40-7.23 (m, 5H), 4.80 (d, *J*=6.1 Hz, 1H), 4.42 (br s, 1H), 4.23 (d, *J*=4.1 Hz, 1H), 3.87 (dd, $J_1$=1.3 Hz, $J_2$=9.4 Hz, 1H), 3.86 (dd, $J_1$=6.1 Hz, $J_2$=9.4 Hz, 1H), 3.79 (dd, $J_1$=1.3 Hz, $J_2$=4.1 Hz, 1H), 3.80 (br s, 1H), 3.62 (dd, $J_1$=9.4 Hz, $J_2$=9.4 Hz, 1H), 3.54 (s, 3H), 3.42 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H) 0.83 (s, 9H), 0.04 (s, 3H), -0.02 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) ***δ:*** 141.2, 128.0, 127.8, 127.6, 106.9, 98.6, 76.5, 76.3, 74.9, 72.4, 63.9, 58.3, 56.5, 29.2, 26.0, 19.5, 18.4, -4.4, -4.8

**LRMS** (CI), *m/z* (relative intensity): 474 ($[M+18]^+$, 100), 457 ($[M+1]^+$, 37), 425 (31), 384 (83), 352 (82), 75 (31)

**HRMS** *m/z* calcd for $C_{23}H_{40}O_7Si$ 474.2887 ($M+NH_4$), found 474.2903(CI)

**75he**

**mp** 72-74 °C

**$[\alpha]^{24}_D$** -23 (c 0.3, chloroform)

**$R_f$** 0.48 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 3476, 2988, 2931, 2856, 1464, 1379, 1203, 1060, 837, 780, 701 $cm^{-1}$

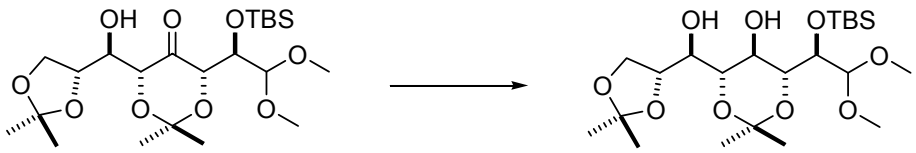
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:*7.42-7.22 (m, 5H), 4.92 (dd, $J_1$=5.1 Hz, $J_2$=5.7 Hz, 1H), 4.28 (d, *J*=4.6 Hz, 1H), 3.96 (d, *J*=4.8 Hz, 1H), 3.86 (d, *J*=5.7 Hz, 1H), 3.84 (dd, $J_1$=1.2 Hz, $J_2$=4.6 Hz, 1H), 3.79 (ddd, $J_1$=2.2 Hz, $J_2$=3.0 Hz, $J_3$=4.8 Hz, 1H), 3.75 (ddd, $J_1$=1.2 Hz, $J_2$=2.2 Hz, $J_3$=5.1 Hz, 1H), 3.73 (ddd, $J_1$=1.2 Hz, $J_2$=1.2 Hz, $J_3$=3.0 Hz, 1H), 3.42 (s, 3H), 3.32 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H) 0.84 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 141.3, 128.4, 127.7, 126.5, 104.9, 99.5, 75.2, 75.1, 73.8, 71.2, 64.0, 56.6, 55.5, 29.8, 26.2, 19.4, 18.5, -4.4, -4.8

**LRMS** (CI), *m/z* (relative intensity): 474 ($[M+18]^+$, 100), 457 ($[M+1]^+$, 73), 410 (76), 384 (20), 367 (30), 259 (8), 161 (22), 132 (10), 75 (52)

**HRMS** *m/z* calcd for $C_{23}H_{40}O_7Si$ 474.2887 ($M+NH_4$), found 474.2901(CI)

**Diol 74hd**




**52hd** **74hd**

To a solution of **52hd** (79 mg, 0.16 mmol, 1.0 eq) in $CH_2Cl_2$ (1.0 mL) AcOH (0.10 mL) and $NaBH(OAc)_3$ (70 mg, 0.33 mmol, 2.0 eq) were added at -20 °C. Reaction was stirred at that temperature for 3 d (TLC controlled reaction).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (x 3).The combined organic layer was washed with NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a crude diols mixture (dr > 1 : 21 *anti* : *syn*) which was purified by flash column chromatography using silica gel (hexane : ethyl acetate) to give pure **74hd** as a colorless oil (45 mg, 0.094 mmol, 57 %, BORSM 92 %) and the starting material **52hd** (30 mg, 0.063 mmol, 38 %)

The same procedure was repeated (96 mg, 0.20 mmol reaction scale) with longer reaction time applied (5 d). The *syn* : *anti* diols were formed in the same ratio as reported above, however yield of the reaction was improved from 57 % to 93 %. The product was isolated by flash column chromatography using silica gel (hexane : ethyl acetate) to give pure **74hd** (89 mg, 0.19 mmol) as a colourless oil.

**$[\alpha]^{24}_D$** +27 (c 1.22, benzene)

**$R_f$** 0.24 (hexanes : ethyl acetate 4 : 1)

**IR**:(KBr) max: 3442, 2985, 2850, 1460, 1382, 1250 $cm^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) $\delta$: 4.56 (d, $J$=6.1 Hz, 1H), 4.51 (ddd, $J_1$=4.8 Hz, $J_2$=7.0 Hz, $J_3$=7.0 Hz, 1H), 4.22 (dd, $J_1$=9.2 Hz, $J_2$=9.3 Hz, 1H), 4.17 (m, 1H), 4.17 (dd, $J_1$=1.2 Hz, $J_2$=9.3 Hz, 1H), 4.17 (br s, 1H), 4.12 (dd, $J_1$=8.1 Hz, $J_2$=8.1 Hz, 1H), 4.06 (dd, $J_1$=1.2 Hz, $J_2$=6.1 Hz, 1H), 3.98 (dd, $J_1$=6.6 Hz, $J_2$=8.1 Hz, 1H), 3.91 (br s, 1H), 3.78 (dd,

$J_1$=5.7 Hz, $J_2$=9.2 Hz, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H), 1.08 (s, 9H), 0.29 (s, 6H)

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.35 (ddd, $J_1$=4.6 Hz, $J_2$=6.8 Hz, $J_3$=6.8 Hz 1H), 4.32 (d, $J$=4.9 Hz, 1H), 4.13 (d, $J$=1.1 Hz, 1H), 4.03 (ddd, $J_1$=2.7 Hz, $J_2$=5.1 Hz, $J_3$=6.8 Hz, 1H), 3.99 (dd, $J_1$=6.8 Hz, $J_2$=11.2 Hz, 1H), 3.97 (dd, $J_1$=4.6 Hz, $J_2$=11.2 Hz, 1H), 3.85 (ddd, $J_1$=1.1 Hz, $J_2$=8.6 Hz, $J_3$=10.0 Hz, 1H), 3.84 (dd, $J_1$=1.0 Hz, $J_2$=10.0 Hz, 1H), 3.80 (dd, $J_1$=1.0 Hz, $J_2$=4.9 Hz, 1H), 3.69 (dd, $J_1$=5.1 Hz, $J_2$=8.6 Hz, 1H), 3.51 (s, 3H), 3.41 (s, 3H), 2.75 (d, $J$=2.7 Hz, 1H),1.43 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H)

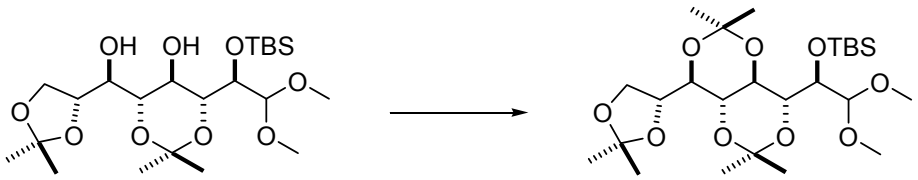
**$^{13}$C NMR** (125 MHz, $C_6D_6$) $\delta$: 109.3, 106.8, 98.9, 76.6, 76.2, 74.1, 73.9, 65.7, 64.2, 56.6, 55.7, 29.6, 27.1, 26.7, 26.0, 19.6, -3.7, -4.1

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 108.8, 106.6, 98.6, 76.1, 75.8, 73.0, 72.8, 65.1, 62.8, 57.6, 56.3, 29.2, 26.7, 26.1, 25.6, 19.5, 18.5, -4.2, -4.6

**LRMS** (CI), *m/z* (relative intensity): 496 ($[M]^+$-2H+$NH_4$, 91), 464 (58), 447 (70), 432 (38), 391 (37), 334 (59), 318 (87), 276 (64), 260 (92), 75 (100)

**HRMS** *m/z* calcd for $C_{22}H_{44}O_9Si$ 496.2942 (M-2H+$NH_4$), found 496.2959 (CI)

**Protected octose (114)**




**74hd** **114**

Diol **74hd** (13 mg, 2.7 $10^{-2}$ mmol, 1.0 eq) was transferred in to the flame dried round bottom flask. *p*-TsOH $H_2O$ (2.8 mg, 0.010 mmol) was added under nitrogen followed by freshly distilled 2,2-dimethoxypropane (1.0 mL). Reaction was stirred at room temperature for 5h (TLC controlled) then was quenched by addition of saturated solution of $NaHCO_3$. The product was extracted with $Et_2O$ (x 3), washed with saturated solution of NaCl and dried with $MgSO_4$. Removal of the solvent under reduced pressure (temperature of water bath was maintained below 30 °C) provided pure protected diol **114** as a white semisolid (12 mg, 2.3 $10^{-2}$ mmol, 85 %).

**$[\alpha]^{24}_D$** +10 (c 1.22, benzene)

**IR** (KBr): 2990, 2931, 2859, 1465, 1380, 1257, 1198, 1173, 1097, 1005, 837, 779 $cm^{-1}$

**$^1$H NMR** (500 MHz, $C_6D_6$) $\delta$: 4.56 (d, $J$=7.9 Hz, 1H), 4.39 (ddd, $J_1$=2.1 Hz, $J_2$=7.0 Hz, $J_3$=8.2 Hz 1H), 4.25 (dd, $J_1$=0.9 Hz, $J_2$=9.4 Hz, 1H), 4.19 (dd, $J_1$=7.3 Hz, $J_2$=8.2 Hz, 1H), 4.17 (dd, $J_1$=9.4 Hz, $J_2$=9.5 Hz, 1H), 4.09 (dd, $J_1$=2.1 Hz, $J_2$=9.5 Hz, 1H), 3.99 (dd, $J_1$=0.9 Hz, $J_2$=7.9 Hz, 1H), 3.83 (dd, $J_1$=7.0 Hz, $J_2$=7.3 Hz, 1H), 3.72 (dd, $J_1$=9.5 Hz, $J_2$=9.5 Hz, 1H), 3.30 (s, 3H), 3.24 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.21 (s, 3H), 1.11 (s, 9H), 0.30 (m, 3H), 0.29 (m, 3H)

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 4.31 (d, $J$=7.9 Hz, 1H), 4.24 (ddd, $J_1$=2.0 Hz, $J_2$=7.0 Hz, $J_3$=7.0 Hz, 1H), 4.06 (dd, $J_1$=7.8 Hz, $J_2$=7.8 Hz, 1H), 3.96-3.88 (m, 4H), 3.63 (d, $J$=7.9 Hz, 1H), 3.58 (ddd, $J_1$=1.3 Hz, $J_2$=8.1 Hz, $J_3$=9.2 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

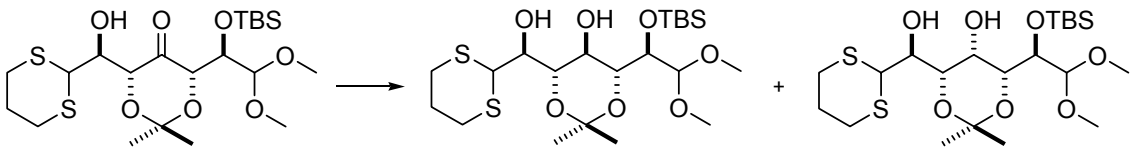
**$^{13}$C NMR** (125 MHz, $C_6D_6$) $\delta$: 109.6, 106.1,100.4, 100.2, 76.5, 75.0, 73.0, 72.1,68.8, 67.1, 65.0, 55.5, 54.4, 30.0, 29.7, 27.1, 26.7, 26.4, 20.1, 19.1, -3.6, -4.1

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 109.4, 105.9,100.0, 99.9, 76.1, 74.4, 72.3, 71.3, 67.9, 66.4, 64.6, 55.8, 55.0, 29.7, 29.4, 26.4, 26.2, 26.0, 20.1, 19.9, -4.1, -4.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 538 ($[M+18]^+$, 4), 521 ($[M+1]^+$, 3), 506 (8), 489 (100), 448 (9), 431 (31), 417 (9), 75 (14)

**HRMS** *m/z* calcd for $C_{25}H_{48}O_9Si$ 521.3140 (M+H), found 521.3140 (CI)

**Diols 74hc and 75hc**




Procedure 1 gave the give a crude diols mixture. Diastereoselectivity of the reaction was measured by integrating peaks at 3.45 ppm and 3.56 ppm and was found to be 1 : 19 *anti* to *syn*. The crude mixture was purified by flash column chromatography using silica gel (hexane : ethyl acetate 8 : 2) to give pure **74hc** as a colorless oil in 85 % yield

Procedure 2 gave the give a crude diols mixture. Diastereoselectivity of the reaction was measured by integrating peaks at 3.45 ppm and 3.56 ppm and was found to be 1 : 3 *anti* to *cis*. The crude mixture was purified by flash column chromatography using silica gel (hexane : ethyl acetate 8 : 2) to give pure **75hc** as a colorless oil in 17 % and **74hc** as a colorless oil in 50 % yield.

**74hc**

**$[\alpha]^{25}_{D}$** +23 (c 1, benzene)

**IR** (KBr): 3457, 2989, 2928, 2902, 1470, 1381, 1250, 1166, 1134, 1075, 1001, 837, 780, 731, 629 $cm^{-1}$

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.93 (br s, 1H), 4.25 (d, *J*=3.8 Hz, 1H), 4.24 (d, *J*=2.6 Hz, 1H), 4.20(br s, 1H), 4.06 (dd, $J_1$=2.6 Hz, $J_2$=7.8 Hz, 1H), 3.90 (dd, $J_1$=7.8 Hz, $J_2$=9.2 Hz, 1H), 3.88 (dd, $J_1$=1.0 Hz, $J_2$=9.2 Hz, 1H), 3.84 (dd, $J_1$=1.0 Hz, $J_2$=3.8 Hz, 1H), 3.80 (dd, $J_1$=9.2 Hz, $J_2$=9.2 Hz, 1H), 3.56 (s, 3H), 3.42 (s, 3H), 3.12-3.02 (m, 2H), 2.84-2.79 (m, 1H), 2.72-2.67 (m, 1H), 2.07-1.96 (m, 2H), 1.45 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H) 0.07 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 106.9, 98.8, 80.9, 76.3, 72.4, 70.6, 65.1, 58.8, 56.6, 47.5, 29.6, 29.2, 28.9, 26.3, 26.1, 19.6, 18.5, -4.1, -4.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 516 ($[M + 18]^+$, 100), 499 ($[M]^+$+1, 21), 484 (19), 467 (35), 435 (40), 409 (51), 119 (11), 75 (17)

**HRMS** *m/z* calcd for $C_{21}H_{42}O_7S_2Si$ 498.2141 ($M^+$), found 498.2164(EI)

**75hc**

$[\alpha]^{25}_D$ -7 (c 1.3, chloroform)

**IR** (KBr): 3456, 2928, 2855, 1465, 1380, 1250, 1200, 1075, 1000, 837, 780, 731, 663 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.38-4.35 (m, 1H), 4.34 (d, *J*=2.9 Hz, 1H), 4.16-4.12 (m, 1H), 3.97-3.94 (m, 2H), 3.90-3.88 (m, 2H), 3.80-3.77 (m, 1H), 3.46 (s, 3H), 3.41 (s, 3H), 3.00-2.86 (m, 3H), 2.84-2.76 (m, 1H), 2.57 (d, *J*=5.1 Hz, 1H), 2.11-2.04 (m, 1H), 1.97-1.87 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H) 0.09 (s, 3H)

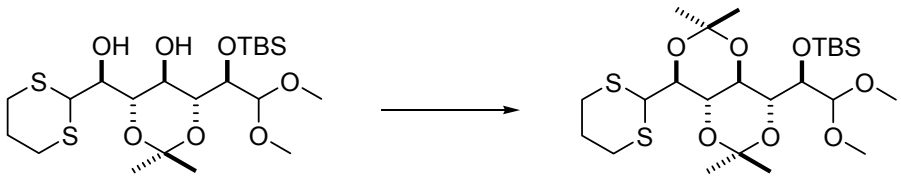
**$^1$H NMR** (500 MHz, $C_6D_6$) *δ:* 4.54 (ddd, $J_1$=2.5 Hz, $J_2$=5.2 Hz, $J_2$=8.5 Hz, 1H), 4.44 (d, *J*=2.4 Hz, 1H), 4.40 (d, *J*=4.2 Hz, 1H), 4.23 (ddd, $J_1$=1.3 Hz, $J_2$=1.5 Hz, $J_2$=7.0 Hz, 1H), 4.15 (dd, $J_1$=1.3 Hz, $J_2$=8.5 Hz, 1H), 4.10 (dd, $J_1$=4.2 Hz, $J_2$=6.1 Hz, 1H), 4.04 (dd, $J_1$=1.5 Hz, $J_2$=6.1 Hz, 1H), 3.36 (d, *J*=7.0 Hz, 1H), 3.24 (s, 3H), 3.09 (s, 3H), 2.66-2.54 (m, 2H), 2.37 (d, *J*=5.2 Hz, 1H), 2.35-2.26 (m, 2H), 1.16-1.45 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.09 (s, 9H), 0.32 (s, 3H) 0.28 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 105.0, 99.4, 74.7, 73.9, 71.9, 70.7, 63.5, 56.7, 55.5, 49.3, 30.1, 29.7, 29.5, 26.2, 26.1, 19.4, 18.5, -4.5, -4.7

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 516 ($[M + 18]^+$, 7), 484 ($[M]^+$+1, 20), 467 (47), 452 (25), 435 (36), 426 (75), 409 (43), 377 (100), 161 (16), 119 (57), 75 (97)

**HRMS** *m/z* calcd for $C_{21}H_{42}O_7S_2Si$ 516.2485 (M + 18), found 516.2495 (CI)

**Protected dialdehyde 115**




**74hc** **115**

Diol **74hc** (0.12 g, 0.24 mmol, 1.0 eq) was transferred in to the flame dried round bottom flask. *p*-TsOH $H_2O$ (4.6 mg, 0.020 mmol, 0.10 eq) was added under nitrogen followed by freshly distilled 2,2-dimethoxypropane (4.0 mL). Reaction was stirred at room temperature for 12 h (TLC controlled) then was quenched by addition of saturated solution of $NaHCO_3$. The product was extracted with $Et_2O$ (x 3), washed with saturated solution of NaCl and dried with $MgSO_4$. Removal of the solvent under reduced pressure (temperature of water bath was maintained below 30 °C) provided crude product which was purified by SCC (hexane : ether 95 : 5) to give pure protected diol **115** as a colorless oil (0.13 g, 0.24 mmol, 98 %).

**$[\alpha]^{24}_D$** +28 (c 0.7, benzene)

**$R_f$** 0.47 (hexane : ethyl acetate 4 : 1)

**IR** (KBr): 2961, 2866, 1463, 1380, 1259, 1197, 1172, 1092, 1052, 881, 798, 678 $cm^{-1}$

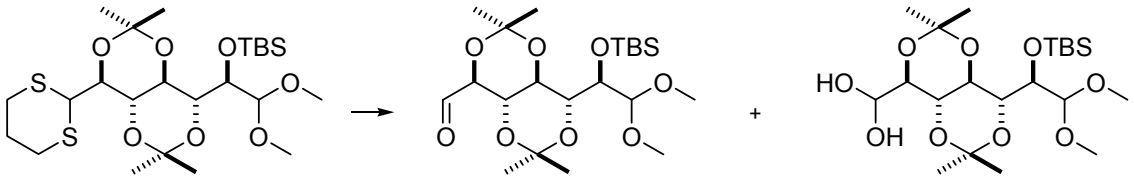
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.30 (d, *J*=8.0 Hz, 1H), 4.13 (dd, $J_1$=1.0 Hz, $J_2$=9.1 Hz, 1H), 4.00 (br s, 1H), 3.97-3.92 (m, 2H), 3.88 (dd, $J_1$=1.4 Hz, $J_2$=9.1 Hz, 1H), 3.63 (d, *J*=8.0 Hz, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.12-3.04 (m, 2H), 2.79-2.72 (m, 1H), 2.70-2.64 (m, 1H), 2.04-1.97 (m, 2H), 1.49 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H) 0.04 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:*105.7, 100.4, 100.3, 79.7, 74.2, 72.2, 67.5, 66.1, 55.7, 55.0, 44.4, 29.7, 29.6, 29.3, 29.2, 26.1, 20.1, 20.0, 18.5, -4.1, -4.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 539 ($[M+1]^+$, 91), 507 (24), 481 (100), 449 (37), 423 (34), 333 (23), 119 (95), 75 (69)

**HRMS** *m/z* calcd for $C_{24}H_{46}O_7S_2Si$ 539.2532 (M+H), found 539.2534 (CI)

**Aldehyde 85**




**115** **85** **116**

To a stirred solution of compound **115** (0.13 g, 0.24 mmol, 1.0 eq) in acetonitrile (3 mL), solution of freshly recrystalized N-bromosuccinimide (0.26 g, 1.4 mmol, 6.0 eq) and silver nitrate (0.27 g, 1.6 mmol, 6.5 eq) in acetonitrile : water (1 : 1; 1 mL) was added at 0 °C. Reaction was stirred at 0 °C for 5 minutes (TLC showed no starting material). Sodium sulphite solution (saturated, 3 mL) was added and the mixture was stirred for 10 min. Then it was filtered over celite, rinsed with $CH_2Cl_2$ and the resulting mixture was extracted with $CH_2Cl_2$ (x 4). The combined organic layer was washed with saturated $NaHCO_3$ solution, NaCl solution and dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure to give a crude aldehyde (95 %). The crude was purified by FCC (hexane : ethyl acetate 15 %) to give the desired product **85** as white semi-solid (81 mg, 0.18 mmol, 76 %). Usually the mixture of **85** and **116** was observed by $^1$H NMR, even though the product was homogenous by TLC. The next step of synthesis – reduction was always carried on using the original mixture from dithiane hydrolysis**.**

**85**

**$[\alpha]^{24}_D$** +7 (c 1, chloroform)

**$[\alpha]^{24}_D$** +13 (c 0.65, benzene)

**IR** (KBr) :2994, 2934, 2856, 1738, 1463, 1379, 1257, 1086, 779 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 9.57 (s, 1H), 4.28 (d, *J*=8.0 Hz, 1H), 4.24 (d, *J*=9.9 Hz, 1H), 4.02 (dd, $J_1$=9.1 Hz, $J_2$=9.3 Hz, 1H), 3.95 (d, *J*=9.3 Hz, 1H), 3.74 (dd, $J_1$=9.1 Hz,

$J_2$=9.9 Hz, 1H), 3.64 (d, $J$=8.0 Hz, 1H), 3.35 (s, 6H), 1.49 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H) 0.04 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 197.5, 105.7, 100.63, 100.58, 76.4, 74.2, 72.2, 67.2, 66.1, 55.7, 55.0, 29.3, 29.2, 26.1, 20.0, 19.9, 18.5, -4.2, -4.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 449 ($[M+1]^+$, 100), 418 (58), 376 (32), 75 (38)

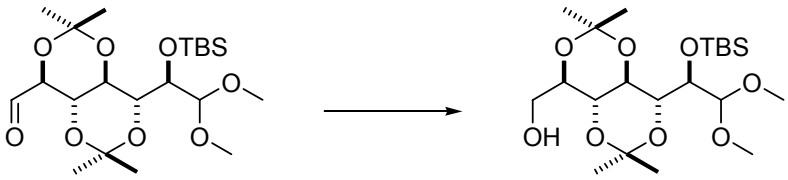
**HRMS** *m/z* calcd for $C_{21}H_{40}O_8Si$ 449.2571 (M+H), found 449.2587 (CI)

**116**

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.56 (d, $J$=12.0 Hz, 1H), 4.29 (dd, $J_1$=7.9 Hz, $J_2$=12.0 Hz, 1H), 4.29(m $J_1$=4.0 Hz, $J_2$=7.6 Hz, 1H), 3.95 (dd, $J_1$=7.9 Hz, $J_2$=9.3 Hz, 1H), 3.94 (br s, 1H), 3.85(d, $J_1$=9.6 Hz, 1H), 3.77 (br s, 1H), 3.75 (dd, $J_1$=9.3 Hz, $J_2$=9.6 Hz, 1H), 3.64 (dd, $J_1$=4.0 Hz, $J_2$=7.6 Hz, 1H), 3.34 (s, 3H), 3.36 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H) 0.05 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 105.8, 100.4, 100.3, 95.8, 74.2, 73.6, 72.3, 66.8, 65.7, 55.8, 55.0, 29.4, 29.3, 26.1, 20.3, 20.2, 18.5, -4.1, -4.6

**Protected heptose 86**




**85** **86**

To a solution of aldehyde **85** (81 mmol, 0.18 mmol, 1.0 eq) in MeOH (5 mL) $NaBH_4$ (27 mg, 0.72 mmol, 4.0 eq) was added at 0 ° C. Reaction was warmed up to r.t and it was stirred at that temperature for 4h (TLC controlled).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with AcOEt (x 4).The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a crude product was purified by passing through short silica gel plug (hexane : ethyl acetate 30 %) to give pure product **86** as a colorless oil (77 mg, 0.17 mmol, 95 %)

**86**

**$[\alpha]^{24}_D$** +4 (0.7, chloroform)

**$R_f$** 0.38 (hexane : ethyl acetate 3 : 2)

**IR** (KBr): 3456 $cm^{-1}$

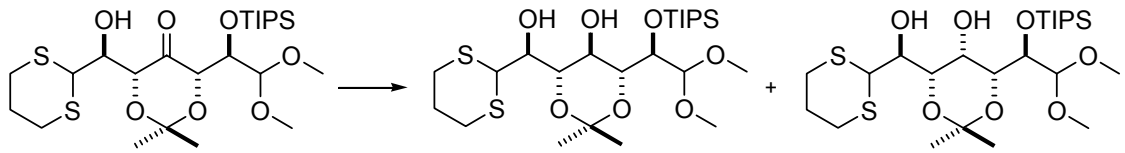
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.31 (d, *J*=8.0 Hz, 1H), 3.96 (dd, $J_1$=9.1 Hz, $J_2$=9.3 Hz, 1H), 3.93 (d, *J*=9.3 Hz, 1H), 3.81 (dd, $J_1$=3.4 Hz, $J_2$=4.7 Hz, $J_3$=9.1 Hz, 1H), 3.70 (dd, $J_1$=3.4 Hz, $J_2$=11.6 Hz, 1H), 3.64 (d, *J*=8.0 Hz, 1H), 3.62 (dd, $J_1$=9.1 Hz, $J_2$=9.3 Hz, 1H), 3.61 (dd, $J_1$=4.7 Hz, $J_2$=11.6 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H) 0.05 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 105.8, 100.3, 100.0, 74.3, 72.9, 72.3, 67.6, 66.0, 62.6, 55.7, 55.0, 29.3, 29.6, 29.3, 26.1, 20.3, 20.2, 18.5, -4.1, -4.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 468 ($[M + 18]^+$, 7), 451 ($[M + 1]^+$, 15), 419 (90), 404 (42), 487 (14), 361 (10), 278 (6), 243 (10), 220 (14), 149 (19), 132 (57), 75 (100)

**HRMS** *m/z* calcd for $C_{21}H_{42}O_8Si$ 451.2727(M + H), found 451.2741(CI, $NH_3$)

**Diols 74hc and 75hc**




Procedure 2 (0.26 g, 0.48 mmol scale) gave the give a crude diols mixture in ratio 1 : 3 *anti* to *syn*. Diastereoselectivity of the reaction was measured by integrating peaks at 3.56 ppm and 3.40 ppm (*syn* to *anti*). The crude mixture was purified by flash column chromatography using silica gel (hexane : ethyl acetate 8 : 2) to give pure **75hc** (46 mg, 8.6 $10^{-2}$ mmol) as a colorless oil in 18 % yield and **74hc** (115 mg, 0.21 mmol) as a colorless oil in 44 % yield.

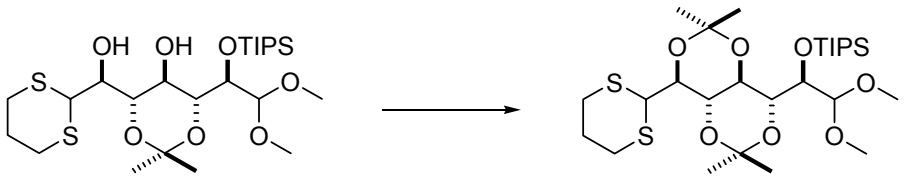
**74hc**

**IR** (KBr): 3462, $cm^{-1}$

**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.89 (br s, 1H), 4.31 (d, *J*=3.5 Hz, 1H), 4.26 (br s, 1H), 4.22 (d, *J*=1.9 Hz, 1H), 4.07 (dd, $J_1$=1.9 Hz, $J_2$=6.6 Hz, 1H), 4.00 (dd, $J_1$=1.0 Hz, $J_2$=3.5 Hz, 1H), 3.92 (dd, $J_1$=1.0 Hz, $J_2$=8.9 Hz, 1H), 3.90 (dd, $J_1$=6.6 Hz, $J_2$=9.4 Hz, 1H), 3.88 (dd, $J_1$=8.9 Hz, $J_2$=9.4 Hz, 1H), 3.57 (s, 3H), 3.45 (s, 3H), 3.16-3.01 (m, 2H), 2.85-2.79 (m, 1H), 2.73-2.64 (m, 1H), 2.12-1.89 (m, 2H), 1.45 (s, 3H), 1.31 (s, 3H), 1.19-0.99 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) ***δ:*** 107.2, 99.0, 81.0, 76.2, 72.6, 70.9, 65.2, 58.5, 57.3, 47.4, 29.6, 29.1, 29.0, 26.3, 19.6, 18.4, 18.3, 12.8

**Protected dialdehyde 117**




**74hc** **117**

Diol **74hc** (39 mg, 0.070 mmol, 1.0 eq) was transferred in to the flame dried round bottom flask. *p*-TsOH $H_2O$ (6.8 mg, 0.040 mmol) was added under nitrogen followed by freshly distilled 2,2-dimethoxypropane (2.0 mL). Reaction was stirred at room temperature for 4h (TLC controlled) then was quenched by addition of saturated solution of $NaHCO_3$. The product was extracted with $Et_2O$ (x 3), washed with saturated solution of NaCl and dried with $MgSO_4$. Removal of the solvent under reduced pressure (temperature of water bath was maintained below 30 °C) provided crude product which was purified by SCC (hexane : ether 95 : 5) to give pure protected diol **117** as a colorless oil (31 mg, 0.050 mmol, 76 %).

**$[\alpha]^{24}_D$** +23 (c 1, benzene)

**IR** (KBr) **:** 2991, 2929, 2897, 2855, 2830, 1463, 1411, 1380, 1255, 1197, 1172, 1089, 1011, 914, 836, 778 $cm^{-1}$

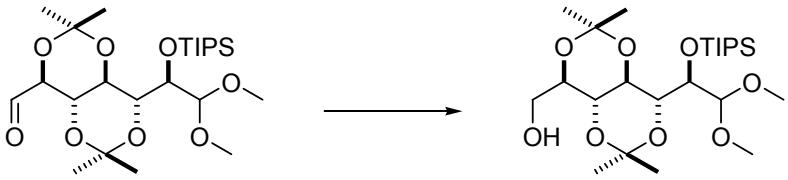
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.28 (d, *J*=7.8 Hz, 1H), 4.13 (dd, $J_1$=1.5 Hz, $J_2$=9.1 Hz, 1H), 4.05 (d, *J*=1.5 Hz, 1H), 4.02 (dd, $J_1$=9.4 Hz, $J_2$=9.4 Hz, 1H) 3.95(dd, $J_1$=1.0 Hz, $J_2$=9.3 Hz, 1H), 3.87 (dd, $J_1$=9.4 Hz, $J_2$=9.4 Hz, 1H), 3.81 (dd, $J_1$=1.0 Hz, $J_2$=7.8 Hz, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 3.10-3.03 (m, 2H), 2.84-2.79 (m, 1H), 2.72-2.67 (m, 1H), 2.07-1.96 (m, 2H), 1.50 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.14-1.04 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:*106.3, 100.4, 100.3, 79.8, 74.5, 72.8, 67.7, 66.1, 55.81, 55.79, 44.6, 29.8, 29.6, 29.2, 26.1, 20.2, 20.1, 18.5, 18.4, 13.0

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 581 ([$M^+$+1], 70), 549 (43), 523 (100), 491 (74), 465 (37), 433 (11), 119 (15), 75 (15)

**HRMS** *m/z* calcd for $C_{27}H_{52}O_7S_2Si$ 581.3002 (M+H), found 581.3005 (CI)

**Protected heptose 119**




**118** **119**

To a solution of aldehyde **118** (16 mmol, 3.3 $10^{-2}$ mmol, 1.0 eq) in MeOH (2 mL) $NaBH_4$ (6.2 mg, 0.16 mmol, 5.0 eq) was added at 0 ° C. Reaction was warm up to room temperature and it was stirred at that temperature for 4h (TLC controlled).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with AcOEt (x 4).The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a crude product was purified by passing through short silica gel plug (hexane : ethyl acetate 30 %) to give pure product **119** as a white semisolid (16 mg, 3.3 $10^{-2}$ mmol, 100 %)

**119**

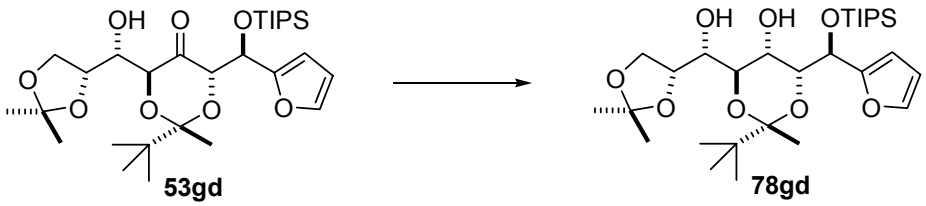
**$[\alpha]^{24}_D$** -2 (c 0.87, benzene)

**IR** (KBr) : 3462 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.30 (d, *J*=7.9 Hz, 1H), 4.01 (dd, $J_1$=9.4 Hz, $J_2$=9.5 Hz, 1H), 3.96 (d, *J*=9.5 Hz, 1H), 3.83 (d, *J*=7.9 Hz, 1H), 3.82 (ddd, $J_1$=3.7 Hz, $J_2$=4.7 Hz, $J_3$=9.3 Hz, 1H), 3.65 (dd, $J_1$=3.7 Hz, $J_2$=12.0 Hz, 1H), 3.56 (dd, $J_1$=9.3 Hz, $J_2$=9.4 Hz, 1H), 3.55 (dd, $J_1$=4.7 Hz, $J_2$=12.0 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.17-1.06 (m, 21H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 106.4, 100.3, 100.1, 74.5, 72.9, 67.9, 66.0, 62.6, 55.9, 55.8, 29.6, 29.3, 20.4, 20.1, 18.5, 18.4, 13.0

**Diol 78gd**




Modified procedure 2 (0.020 mmol scale) with $NaBH(OAc)_3$ as a reducing reagent gave a crude product which was purified by PTLC (hexanes : ethyl acetate 3 : 2) to give *syn* diol **78gd** (7.9 mg, 75 %) as a colorless liquid and *anti* diol (1.1 mg, 11 %) as a colorless oil. Diastereoselectivity of the reaction was measured on crude product by $^1$H NMR by integrating the peaks at 5.10 ppm ($J$=7.3 Hz) and 5.01 ppm ($J$=5.0 Hz) and was found to be 1 : 18 *anti* to *syn*. Only major isomer was characterized.

**78gd**

**$[\alpha]^{24}_D$** +10 (c 0.4 chloroform)

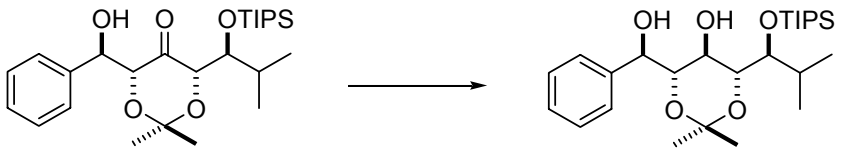
**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.33 (m, 1H), 6.29 (m, 1H), 6.28 (m, 1H), 5.10 (d, $J$=7.3 Hz, 1H), 4.29 (ddd, $J_1$=4.1 Hz, $J_2$=6.7 Hz, $J_3$=7.3 Hz, 1H), 4.21 (ddd, $J_1$=3.5 Hz, $J_2$=5.1 Hz, $J_3$=5.9 Hz, 1H), 4.12 (dd, $J_1$=3.5 Hz, $J_2$=7.3 Hz, 1H), 4.04 (dd, $J_1$=7.3 Hz, $J_2$=8.1 Hz, 1H), 3.85 (dd, $J_1$=7.3 Hz, $J_2$=8.1 Hz, 1H), 3.81 (dd, $J_1$=5.1 Hz, $J_2$=8.0 Hz, 1H), 361 (ddd, $J_1$=4.0 Hz, $J_2$=5.0 Hz, $J_3$=8.0 Hz, 1H), 3.29 (d, $J$=5.9 Hz, 1H), 2.47 (d, $J$=5.0 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.12 (s, 3H), 1.03-0.90 (m, 21H), 0.88 (s, 9H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 154.6, 141.7, 110.4, 109.4, 108.9, 105.0, 78.3, 75.9, 72.7, 71.4, 68.4, 67.7, 66.4, 41.0, 26.7, 25.6, 25.5, 18.3, 18.2, 18.0, 12.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 557 ($[M+1]^+$, 2), 400 (94), 365 (100), 283 (33), 227 (17), 190 (57), 118 (115), 58 (28)

**HRMS** *m/z* calcd for $C_{29}H_{52}O_8Si$ 557.3510 (M+H), found 557.3515 (CI)

**Diol 74fg**




**52fg** **74fg**

To a solution of **52fg** (33 mg, 7.1 $10^{-2}$ mmol) in $CH_2Cl_2$ (0.25 mL), AcOH (0.050 mL) and $NaCNBH_3$ (10 mg, 16 $10^{-2}$ mmol, 2.2 eq) were added at -20 °C. Reaction was stirred at that temperature for 7 h (TLC controlled).The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (x 3).The combined organic layer was washed with NaCl, dried over anhydrous $MgSO_4$ and concentrated to give a crude diols mixture (dr > 1 : 8 *anti* : *syn*) which was purified by flash column chromatography using silica gel (hexane : ethyl acetate) to give pure **74fg** (21 mg, 4.6 $10^{-2}$ mmol, 65 %) as a colorless oil which solidified at low temperature.

**74fg**

**$[\alpha]^{24}_D$** +16 (c 1, chloroform)

**$R_f$** 0.45 (hexane : ethyl acetate 7 : 3)

**IR** (KBr): 3459, 2942, 2867, 1464, 1423, 1381, 1256, 1203, 1068, 1070, 882, 699 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.41-7.36 (m, 2H), 7.31-7.25 (m, 3H), 4.84 (d, *J*=5.4 Hz, 1H), 3.93 (dd, $J_1$=5.5 Hz, $J_2$=9.4 Hz, 1H), 3.76 (dd, $J_1$=4.3 Hz, $J_2$=5.5 Hz, 1H), 3.69 (dd, $J_1$=5.5 Hz, $J_2$=9.2 Hz, 1H), 3.41 (dd, $J_1$=9.2 Hz, $J_2$=9.4 Hz, 1H), 3.34 (br s, 1H), 3.39 (br s, 1H), 1.94-1.84 (m, 1H), 1.39 (s, 3H), 1.28 (s, 3H), 1.04-0.98 (s, 21H), 0.94 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 140.7, 128.0, 127.9, 127.7, 98.9, 81.0, 75.5, 75.1, 71.5, 67.8, 34.0, 29.4, 19.3, 18.9, 18.4, 18.2, 16.2, 13.1

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 467 ($[M+1]^+$, 100), 449 (20), 409 (25), 391 (8), 347 (14), 275 (36), 229 (14)

**HRMS** *m/z* calcd for $C_{26}H_{46}O_5S_2Si$ 467.3193 (M+H), found 467.3196 (CI)

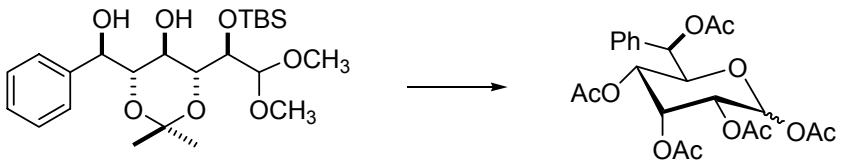
### 3.9 Synthetic applications

Reduced bis aldol products were subjected for deprotection using acidic conditions. Further transformations of analytical samples of corresponding free sugar or methyl glycosides led to the protected (acetylated) carbohydrates which were then characterized.

**General procedure A1:**

To the stirred solution of diol (1 eq) in MeOH, concentrated HCl (approx. 0.1 – 0.3 eq) was added followed by addition of $H_2O$ (0.1 eq). The reaction was heated under reflux for 1 - 2 h, and then it was cooled down. Solvent was evaporated a few times with benzene and residue was dried on high vac. Analytical sample was further transferred into the corresponding acetate derivative by using acetic anhydride and sodium acetate as a catalyst.

**Protected 6-C-phenyl-D-glycero-D-allo-hexopyranose (83)**




General procedure A1 gave the mixture of β and α anomers. Purification by PTLC (hexane : ethyl acetate 7 :3; x 2) provided partial separation of the products. One of them was fully characterized as β-83.

**β-83**

**$[\alpha]^{26}_{D}$** -22 ± 1 (c 0.12, benzene)

**$R_f$** 0.64 (dichloromethane : methanol 19 : 1)

**IR:** 2965, 1751, 1372, 1218, 1066, 915, 721 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.33-7.27 (m, 3H), 7.23-7.21 (m, 2H), 5.99 (d, *J*=8.6 Hz, 1H, CH-C1), 5.91 (d, *J*=2.7H, 1H, CH-C6), 5.58 (dd, $J_1$=2.9 Hz, $J_2$=5.8 Hz, 1H, CH-C3), 4.81 (dd, $J_1$=2.9 Hz, $J_2$=8.6 Hz, 1H, CH-C2), 4.68 (dd, $J_1$=2.9 Hz, $J_2$=10.0 Hz, 1H, CH-C4), 4.41 (dd, $J_1$=2.7 Hz, $J_2$=10.0 Hz, 1H, CH-C5), 2.13 (s, 6H), 2.11 (s, 3H), 1.97 (s, 3H), 1.86 (s, 3H)

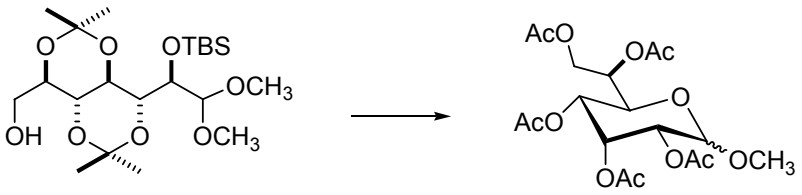
**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 170.11, 170.07, 169.4, 169.2, 169.0, 135.0, 128.8, 128.6, 127.7, 90.3, 74.0, 73.9, 68.5, 68.1, 66.9, 21.3, 21.2, 21.0, 20.72, 20.68

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 484 ($[M+NH_4]^+$, 100), 456 (17), 407 (32), 382 (56), 317 (7), 209 (24), 58 (5)

**HRMS** *m/z* calc for $C_{22}H_{26}O_{11}$ 489.1373 (M+Na), found 489.1334 (Maldi-Tof)

**HRMS** *m/z* calc for $C_{22}H_{26}O_{11}$ 484.1819 ($M+NH_4$), found 484.1827 (CI)

**D-glycero-D-alloheptose hexaacetate (88)**




**86** **88**

General procedure A1 gave the mixture of β and α anomers. Purification by PTLC (hexane : ethyl acetate 7 :3; x 2) provided partial separation of the products. One of them was fully characterized as β-88.

**β-88**

**$[\alpha]^{24}_D$** -22 (c 0.12, chloroform)

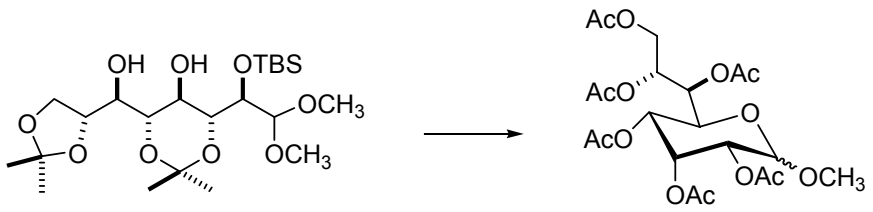
**$^1$H NMR (500 MHz, $CDCl_3$) *δ:*** 5.61 (dd, $J_1$=3.1 Hz, $J_2$=6.1 Hz, 1H, CH-C3), 5.24 (ddd, $J_1$=2.7 Hz, $J_2$=4.3 Hz, $J_3$=7.3 Hz 1H, CH-C6), 5.00 (dd, $J_1$=3.1, $J_2$=10.3 Hz, 1H, CH-C4), 4.82 (dd, $J_1$=3.1 Hz, $J_2$=8.2 Hz, 1H, CH-C2), 4.66 (d, $J$=8.2 Hz, 1H, CH-C1), 4.32 (dd, $J_1$=4.3 Hz, $J_2$=11.9 Hz, 1H, CH-C7), 4.17 (dd, $J_1$=7.3 Hz, $J_2$=11.9 Hz, 1H, CH-C7), 4.01 (dd, $J_1$=2.7 Hz, $J_2$=10.3 Hz, 1H, CH-C5), 3.48 (s, 3H $OCH_3$-C1), 2.14 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 2.01 (s, 6H)

**$^{13}$C NMR (125 MHz, $CDCl_3$) *δ:*** 170.3, 169.8, 169.3, 168.8 (2 x), 99.6 (C1), 71.5 (C5), 70.2 (C6), 68.9 (C2), 68.6 (C3), 67.3 (C4), 61.8 (C7), 56.7 (OMe), 21.2, 20.94, 20.92, 20.9, 20.8

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 480($[M+NH_4]^+$, 42), 452 (100), 403 (24), 378 (27)

**HRMS** *m/z* calcd for $C_{19}H_{26}O_{13}$ 480.1717($M+NH_4$), found 480.1727 (CI, $NH_3$)

**D-erythro-D-allo-octopyranose hexaacetate (90)**




**74hd** **90**

Protected compound **74hd** (25 mg**,** 0.050 mmol) was dissolved in MeOH (2.0 mL). HCl (0.20 mL) and $H_2O$ (0.20 mL) were added and the reaction was heated under reflux for 1.5 h. Then the solution was cooled down to r.t. and solvent was removed under reduced pressure, traces of $H_2O$ was removed as an azeotropic mixture with benzene and then dried on high vacuum to yield viscous, yellowish product. The crude carbohydrate was then dissolved in freshly distilled acetic anhydride (3.0 mL), sodium acetate (5.0 mg, 0.060 mmol).The resulting mixture was heated to 90 °C for 3 h and the reaction was quenched with the mixture of ice and $NaHCO_3$ salt. The mixture was extracted with ethyl acetate (x 4), and then combined organic layers were washed with brine. The organic phase was dried over anhydrous $MgSO_4$, concentrated to get a crude product. The isomeric ratio was measured by $^1$H NMR by integrating peaks at 3.47 and 3.40 ppm and was found to be 3 : 1 α and β anomers. The crude was purified by PTLC (hexane : ethyl acetate 3 : 7) to yield the product **90** (6.0 mg, 0.012 mmol, 23 %) as a mixture protected of α and β anomers. Further purification provided isolation of major component of this mixture identify as β anomer.

**<u>β-90</u>**

**$[\alpha]^{24}_D$** -24 ± 1 (c 0.11, benzene)

**$[\alpha]^{24}_D$** -25 ± 1(c 0.11, chloroform)

**Rf** 0.46 (dichloromethane : methanol 19 : 1)

**IR** (KBr): 2954, 1749, 1369, 1221, 1037, 601 $cm^{-1}$

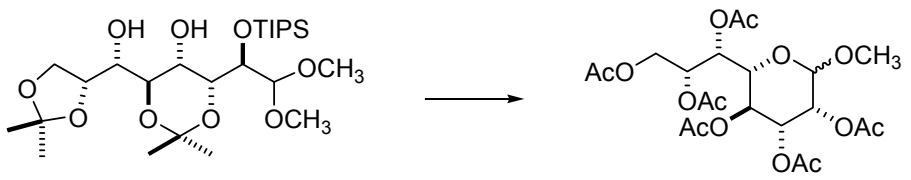
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 5.62 (dd, $J_1$=3.0 Hz, $J_2$=3.0 Hz, 1H, CH-C3), 5.36 (dd, $J_1$=3.1 Hz, $J_2$=5.2 Hz, 1H, CH-C6), 5.21 (ddd, $J_1$=2.5 Hz, $J_2$=5.2 Hz, $J_3$=6.9 Hz, 1H, CH-C7), 4.98 (dd, $J_1$=2.7 Hz, $J_2$=10.2 Hz, 1H, CH-C4), 4.84 (dd, $J_1$=3.0 Hz, $J_2$=8.2 Hz, 1H, CH-C2), 4.65 (d, $J$=8.2 Hz, 1H, CH-C1), 4.41 (dd, $J_1$=2.5 Hz, $J_2$=12.3 Hz, 1H, CH-C8), 4.20 (dd, $J_1$=6.9 Hz, $J_2$=12.3 Hz, 1H, CH-C8), 4.05 (dd, $J_1$=3.1 Hz, $J_2$=10.2 Hz, 1H, CH-C5), 3.47 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H,), 2.00 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 170.90, 170. 84, 170.07, 169.91, 169.74, 169.36, 99.88, 71.61, 70.36, 70.10, 69.82, 68.69, 67.69, 62.47, 56.80, 21.07, 21.06, 20.97, 20.90, 20.88, 20.71

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 524 ($[M+NH_4]^+$, 100), 466 (5), 450 (28), 406 (6), 77 (19), 60 (22)

**HRMS** *m/z* calcd for $C_{21}H_{30}O_{14}$ 524.1979 ($M+NH_4$), found 524.1989 (CI, $NH_3$)

**Protected D-threo-L-manno-octose (101)**




**78hd** **101**

General procedure A1 gave the mixture of β and α anomers. Purification by PTLC (hexane : ethyl acetate 7 :3) provided partial separation of the products. One of the acetylated octose was fully characterized as β-101.

**β-101**

$[\alpha]^{26}_{D}$ –49 (c 0.1, chloroform)

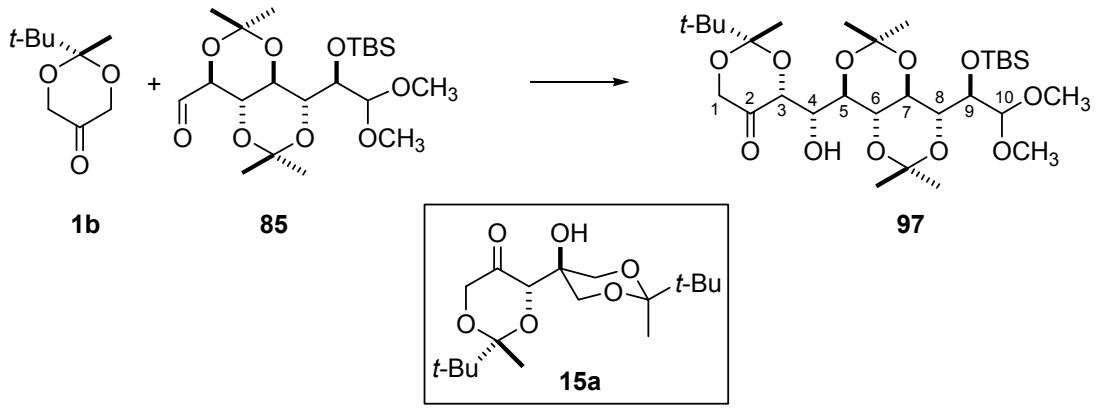
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 5.50 (ddd, $J_1$=3.9 Hz, $J_2$=5.8 Hz, $J_3$=6.2 Hz, 1H, CH-C7), 5.29-5.24 (m, 2H, CH-C3, CH-C4), 5.22 (dd, $J_1$=3.1 Hz, $J_2$=5.8 Hz, 1H, CH-C6), 5.15 (dd, $J_1$=1.9 Hz, $J_2$=2.8 Hz, 1H, CH-C2), 4.66 (d, $J$=1.9 Hz, 1H, CH-C1), 4.39 (dd, $J_1$=3.9 Hz, $J_2$=12.1 Hz, 1H, CH-C8), 4.15 (dd, $J_1$=6.2 Hz, $J_2$=12.1 Hz, 1H, CH-C8), 3.94 (ddd, $J_1$=0.5 Hz, $J_2$=3.1 Hz, $J_3$=7.5 Hz, 1H, CH-C5), 3.37 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.057 (s, 3H), 2.053 (s, 3H), 1.97 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 170.8, 170.3, 170.12, 170.10, 169.95, 169.88, 98.5 (C1), 70.6 (C5), 70.3 (C6), 69. 42 (C2, C3), 69.36 (C7), 67.27 (C4), 62.7 (C8), 55.7 (OMe), 21.1, 20.99, 20.97, 20.95, 20.93, 20.92

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 524 ($[M+NH_4]^+$, 100), 475 (3), 466 (2), 380 (3) (28), 236 (2), 77 (4), 58 (4)

**HRMS** *m/z* calcd for $C_{21}H_{30}O_{14}$ 524.1979 ($M+NH_4$), found 524.1989 (CI, $NH_3$)

**Protected decose (97)**




2-*tert*-Butyl-2-methyl-1,3-dioxan-5-one (**1b**) (26 mg, 0.15 mmol, 2.2 eq) was added to the flamed dried vial charged with (*S*)-proline (7.7 mg, 7.0 $10^{-2}$ mmol, 1.0 eq) and LiCl (1.0 eq). Aldehyde **85** (30 mg, 7.0 $10^{-2}$ mmol, 1.0 eq) was added and DMSO (0.15 mL) and all the reactants were premixed at room temperature for 15 min. The reaction mixture was kept at 4 °C for 4 days. Then water was added and the compound was extracted with AcOEt (x 4), washed with brine and dried with $MgSO_4$. The removal of the solvent under reduced pressure provided crude compound. Careful inspection of the crude $^1$H NMR indicated the formation of three compounds: aldol condensation product, dioxanone adduct and aldol products whit the characteristic peaks at 5.88 ppm, 4.73 ppm and 4.44 ppm in 1 : 5 : 9 ratio. The crude was purified by PTLC (hexane : AcOEt) to provide the dimer of dioxanone (**15a**) (7.8 mg, 2.2 $10^{-3}$ mmol, 30 %) as a yellowish oil and aldol adduct **97** (9.0 mg, 1.4 $10^{-3}$ mmol, 25 %) as a colourless oil. Product of aldol condensation reaction was not isolated.

**97**

**$[\alpha]^{24}_D$** -14 (c 0.42, chloroform)

**IR** (KBr): 3525, 2960, 2857, 1737, 1470, 1381, 1258, 1197, 1094, 1009, 836, 780 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.44 (d, *J*=3.2 Hz, 1H, CH-C3), 4.31 (dd, $J_1$=1.0 Hz, $J_2$=17.7 Hz, 1H, CH-C1), 4.28 (d, *J*=8.0 Hz, 1H, CH-C10), 4.21 (dd, $J_1$=3.2 Hz, $J_2$=7.3

Hz, 1H, CH-C4), 4.14 (d, $J$=17.7 Hz, 1H, CH-C1), 4.06 (dd, $J_1$=7.3 Hz, $J_2$=9.1 Hz, 1H, CH-C5), 3.99 (dd, $J_1$=9.3 Hz, $J_2$=9.3 Hz, 1H, CH-C7), 3.95 (dd, $J_1$=1.0 Hz, $J_2$=9.3 Hz, 1H, CH-C8), 3.76 (dd, $J_1$=9.1 Hz, $J_2$=9.3 Hz, 1H, CH-C6), 3.63 (dd, $J_1$=1.0 Hz, $J_2$=8.0 Hz, 1H, CH-C9), 3.36 (s, 3H), 3.35 (s, 3H), 3.23 (br s, 1H, OH-C4), 1.51 (s, 6H), 1.39 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.05 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H)

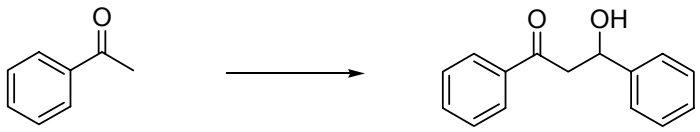
**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 207.1, 105.9, 103.7, 100.6, 100.3, 77.3, 76.2, 74.3, 72.3, 71.9, 69.9, 69.6, 65.8, 56.0, 55.0, 40.3, 29.4, 26.1, 25.5, 20.32, 20.27, 18.5, 15.9, -4.1, -4.6

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 621($[M+H]^+$, 8), 589 (18), 449 (42), 417 (21), 376 (17), 345 (28), 262 (27), 173 (100), 159 (5), 118 (23), 75 (28)

**HRMS** *m/z* calcd for $C_{30}H_{56}O_{11}Si$ 621.3670 (M+H), found 621.3687 (CI, $NH_3$)

### 3.10 Miscellaneous studies

### 3-Hydroxy-1,3-diphenylpropan-1-one (118)




**117** **118**

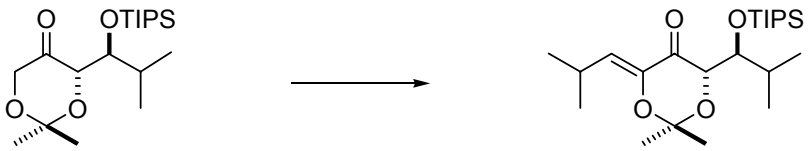
Magnesium iodide (0.34 g, 1.2 mmol, 1.2 eq), acetophenone **(117)** (0.12 g, 1.0 mmol, 1.0 eq) and benzaldehyde (0.11 g, 1.0 mmol, 1.0 eq) were dissolved in $CH_2Cl_2$ (5 mL). $(i\text{-}Pr)_2EtN$ (0.23 mL, 1.3 mmol, 1.3 eq) was added slowly under nitrogen and reaction mixture was stirred for 0.5 h and after this time diluted HCl was added. Solvent was evaporated and residue was extracted with AcOEt (x 2).Solvent was evaporated and residue was extracted with AcOEt (x 2). Combined organic layers were washed with saturated NaCl and dried with $MgSO_4$. Solvent was evaporated to afford crude product which was purified by FCC (hexane : ethyl acetate 9 : 1) to give pure **118** (0.20 g, 0.88 mmol) in 87 % yield as a liquid.

**$R_f$** 0.19 (hexane : ethyl acetate 4 : 1)

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 7.96-7.92 (m, 2H), 7.59-7.54 (m, 1H), 7.47-7.40 (m, 4H), 7.39-7.33 (m, 2H), 7.32-7.26 (m, 1H), 5.33 (dd, $J_1$=5.3 Hz, $J_2$=6.7 Hz, 1H), 3.60 (br s, 1H), 3.36 (d, *J*=5.3 Hz, 1H), 3.35 (d, *J*=6.7 Hz, 1H)

**$^{13}$C NMR** (125 MHz, $C_6D_6$) *δ:* 200.3, 133.8, 128.9, 128.7, 128.3, 127.8, 125.9, 70.2, 47.6

**Aldol condensation product 41**

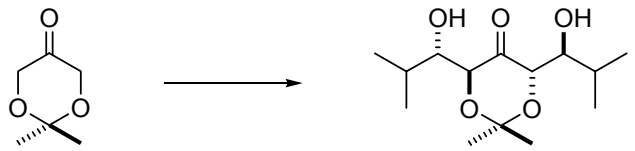



**36** **41**

Magnesium iodide (43 mg, 0.15 mmol, 1.3 eq), isobutyraldehyde (9.2 mg, 0.13 mmol, 1.2 eq) and starting TIPS protected β-hydroxyketone **36**(41 mg, 0.12 mmol, 1.0 eq) were dissolved in $CH_2Cl_2$ (1 mL). $(i\text{-}Pr)_2EtN$ (0.020 mL, 0.13 mmol, 1.2 eq) was added slowly under nitrogen and reaction mixture was stirred for 0.5 h and after this time concentrated pH 7 buffer was added. Solvent was evaporated and residue was extracted with AcOEt (x 2). Combined organic layers were washed with saturated NaCl and dried with $MgSO_4$. Solvent was evaporated to afford crude product which was purified by FCC (hexane : ethyl acetate 5 %) to give α,β-unsaturated ketone **41** (7.0 mg, 0.020 mmol, 15 %) and recovered starting material (10 mg, 24 %).

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 5.78 (d, *J*=9.4 Hz, 1H), 4.45 (s, 1H), 4.07(d, *J*=6.7 Hz, 1H), 2.74-2.64 (m, 1H), 2.02-1.91 (m, 1H), 1.54 (s, 3H), 1.47 (s, 3H), 1.12-1.03 (m, 21H), 1.00-0.94 (m, 9H), 0.83 (d, *J*=6.6 Hz, 3H)

**4-(*S*)-6-(*S*)-4,6-bis[(*S*)-1-hydroxy-2-methylpropyl]-2,2-dimethyl-1,3-dioxan-5-one (119)**




**1a** **119**

*Reaction was done based on the modified procedure B1*

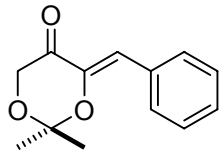
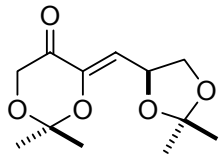
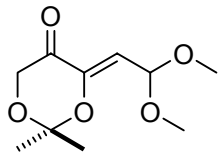
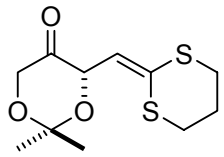
Triethylamine (0.28 mL, 2.0 mmol, 2.0 eq) was dissolved in $CH_2Cl_2$ (5 mL), and the solution was cooled to 0 °C. Dicyclohexylboron chloride (1.0 mL, 1.0 M solution in hexane, 1.0 mmol) was added, and the solution was stirred for 15 min. Next, dioxanone **1a** (0.13 g, 1.0 mmol, 1.0 eq) was added, and, after stirring for 15 min, isobutyraldehyde (72 mg, 1.0 mmol, 1.0 eq) was added. After stirring for another 15 min, triethylamine (0.28 mL, 2.0 mmol, 2.0 eq) was added followed by addition of dicyclohexylboron chloride (1.0 mL, 1.0 M solution in hexane, 1.0 mmol) and, after 15 min, aldehyde isobutyraldehyde (79 mg, 1.1 mmol, 1.1 eq). After stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer (20 mL) and extracted with diethyl ether (x 3). The extracts were washed with brine (x 2) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol (18 mL) and cooled to 0 °C. Concentrated pH 7 buffer (6 mL) and hydrogen peroxide (6 mL, 30%) were next added. The solution was stirred at 0 °C for 3 h, $Et_2O$ (150 mL) was added, and the solution was washed with saturated $NaHCO_3$ (x 2), brine (15 mL) and was dried with $MgSO_4$. The solvents were removed, and the diastereoselectivity of the reaction was determined by $^1H$ NMR on the crude product. Four isomers were detected in the ratio of 83 : 9 : 6 : 2. The major product was isolated by FCC (hexane : ethyl acetate), which gave a colorless liquid (222 mg, 0.81 mmol, 81 %). Only the major isomer **119** was characterized.

**IR** (KBr): 3509, 1733 $cm^{-1}$

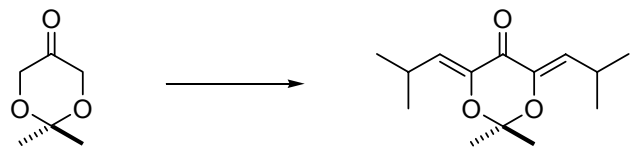
**$^{1}$H NMR** (500 MHz, $CDCl_3$) *δ:* 4.09 (d, *J*=7.4 Hz, 2H), 3.96 (ddd, $J_1$=2.9 Hz, $J_2$=3.8 Hz, $J_3$=7.4 Hz, 2H), 2.93 (d, *J*=2.9 Hz, 2H), 2.04-1.97 (m, 2H), 1.43 (s, 3H), 0.98 (d, *J*=6.9 Hz, 1H), 0.90 (d, *J*=6.9 Hz, 1H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 216.9, 101.6, 74.6, 74.1, 28.9, 24.0, 19.5, 15.6

### 3.11 Side products of the *(S)*-proline catalyzed aldol reaction

| Structure | $^{1}$H NMR ($\delta$ ppm $CDCl_3$) | $^{13}$C NMR ($\delta$ ppm $CDCl_3$) |
|---|---|---|
|  | 7.74-7.73 (m, 2H), 7.36-7.29 (m, 3H), 6.73 (s, 1H), 4.43 (s, 2H), 1.66 (s, 6H) | 191.2, 146.0, 133.7, 131.0, 129.1, 128.7, 115.0, 101.2, 67.7, 25.6 |
|  | 5.88 (d, *J*=7.5 Hz, 1H), 5.15 (d, *J*=7.5 Hz, 1H), 4.33 (s, 2H), 3.32 (s, 6H), 1.54 (s, 6H) $[\alpha]^{24}_{D}$ + 11 (c 0.95, $CHCl_3$) | 190.4, 147.3, 115.5, 109.7, 101. 2, 70.4, 69.1, 67.4, 26.7, 26.0, 25.4, 25.2 |
|  | 5.88 (d, *J*=7.5 Hz, 1H), 5.15 (d, *J*=7.5 Hz, 1H), 4.33 (s, 2H), 3.32 (s, 6H), 1.54 (s, 6H) | 190.9, 147.5, 112.1, 101.4, 97.5, 67.5, 53.1, 25.4 |
|  | 5.81 (d, *J*=7.7 Hz, 1H), 5.20 (d, *J*=7.7 Hz, 1H), 4.29 (d, *J*=17.2 Hz, 1H), 4.05 (d, *J*=17.2 Hz, 1H), 2.97-2.10 (m, 4H), 2.19-2.10 (m, 2H), 1.54 (s, 3H), 1.42 (s, 3H) | 207.4, 140.2, 120.2, 101.6, 72.3, 67.0, 29.3, 29.0, 24.4, 24.2, 24.1 |

**Dienone 120**



**1a** **120**

Dioxanone **1a** (12 mg, 0.090 mL) was added to the flame dried vial charged with $Al_2O_3$ (1.0 g), isobutyraldehyde (32 mg, 0.45 mmol, 5.0 eq).$CH_2Cl_2$ (5.0 mL) Was added and the reaction was stirred at rt for 16 h. The solution was filtered through Celite and the solvent was evaporated to provide the crude product which was purified by SCC (hexane : ethyl acetate 4 : 1) to give a pure compound **120** (17 mg, 0.070 mmol, 77 %) as a pale yellow oil.

**IR** (KBr):1736 $cm^{-1}$

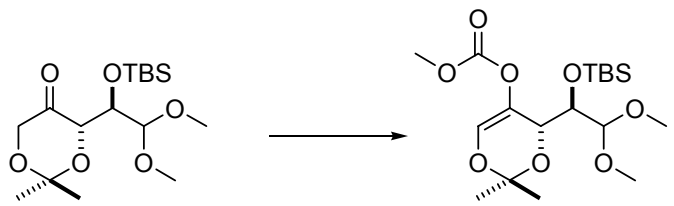
**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$: 5.94 (d, $J$=9.5 Hz, 2H), 2.77-2.67 (m, 2H), 1.55 (s, 6H), 1.00 (d, $J$=6.8 Hz, 12H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$: 178.3, 144.5, 127.2, 100.6, 26.1, 24.7, 22.3, 22.0

**LRMS** (CI, $NH_3$), *m/z* (relative intensity): 239($[M+H]^+$, 100), 216 (37), 188 (36)

**HRMS** *m/z* calcd for $C_{14}H_{22}O_3$ 239.1647 (M+H), found 239.1641 (CI, $NH_3$)

**Compound 16**




**51h** **16**

*n*-BuLi (0.20 mL, 0.46 mmol, 2.3 M solution in hexanes, 2.4 eq) was added dropwise to a stirred solution of DIA (0.090 mL, 0.50 mmol, 2.6 eq) in THF (3 mL) at 0 °C under nitrogen. After 30 min solution was cooled down to -78 °C and solution of **51h** (67 mg, 0.19 mmol, 1.0 eq) in THF was added slowly and the mixture was stirred for 2 h at -78 °C. Methyl cyanoformate (59 mg, 0.060 mL, 0.7 mmol, 3.6 eq) was added then and after 45 min the reaction was quenched with potassium carbonate (40 %; 20 mL) and warmed up to room temperature. The product was extracted with chloroform (x 3). The combined organic layers were rinsed with saturated NaCl, dried over $MgSO_4$, concentrated to give a crude product. Diastereoselectivity of the reaction was measured on the crude product by integration of peaks in $^1$H NMR at 6.55 ppm ($J$=1.1 Hz) and 6.56 ppm ($J$=1.8 Hz) and was found to be 32.3 : 1 (dr > 97). The crude was purified by passing it through silica plug to afford the pure product **16** (63 mg, 0.15 mmol, 80 %).

**Major component of the reaction mixture**

**IR** (KBr) done on the mixture of two isomers: 2995, 2926, 2856, 1766, 1695, 1441, 1253, 990, 780, 745 $cm^{-1}$

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 6.55 (d, $J$=1.1 Hz, 1H), 4.57 (dd, $J_1$=1.1 Hz, $J_2$=1.1 Hz, 1H), 4.37 (d, $J$=7.2 Hz, 1H), 3.86 (dd, $J_1$=1.1 Hz, $J_2$=7.2 Hz, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 3.30 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H) 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 155.1, 136.0, 130.1, 105.8, 100.5, 73.7, 70.0, 55.6, 55.5, 54.6, 27.4, 26.0, 21.2, 18.5, -4.2, -4.6

**LRMS** (CI), *m/z* (relative intensity): 424 ($[M+18]^+$, 78), 392 (100), 366 (12), 334 (26), 187 (60), 75 (55)

**HRMS** *m/z* calcd for $C_{18}H_{34}O_8Si$ 424.2362 ($M+NH_4$), found 424.2362(CI)

**Minor component of the reaction mixture**

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ:* 6.56 (d, *J*=1.8 Hz, 1H), 4.61 (dd, $J_1$=1.6 Hz, $J_2$=1.8 Hz, 1H), 4.34 (d, *J*=7.3 Hz, 1H), 3.79 (s, 3H), 3.71 (dd, $J_1$=1.6 Hz, $J_2$=7.3 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H) 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H)

**$^{13}$C NMR** (125 MHz, $CDCl_3$) *δ:* 155.2, 135.9, 129.8, 105.6, 100.2, 71.1, 69.1, 56.1, 55.6, 54.6, 27.7, 26.1, 21.2, 18.6, -3.8, -5.2

## 3.12 References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